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(54) Title: PYRROLIDINONES

(57) Abstract

Novel pyrrolidinones are described which inhibit PDE IV and TNF.

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PYRROLIDINONES

Field of Invention

The present invention relates to novel pyrrolidinones, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

It is now understood that the symptoms of chronic asthma are the manifestations of three distinct processes:

1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperreactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987.

The agents currently available (β-adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none of them modify all three phases of asthma and nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs (Robison et al., Cyclic AMP Academic Press, New York, pgs. 17-47, 1971; Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, pgs. 17-29, 1973). When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated which converts Mg^{2+}-ATP to cAMP at an accelerated rate. The actions of cAMP are terminated by cyclic nucleotide phosphodiesterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-AMP, an inactive metabolite.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including:

1) airway sooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit PDE should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cyclic AMP breakdown in airway smooth muscle and inflammatory cells. Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd. (1989). Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case in vivo. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid

spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sacroidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

TNF has been implicated in various roles with the human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). It has now been discovered that monokines, specifically TNF, are implicated in the infection of T lymphocytes with HIV by playing a role in maintaining T lymphocyte activation. Furthermore, once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. It has also been discovered that monokines, specifically TNF, are implicated in activated T cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by ihibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of

the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

It has now been discovered that monokines are implicated in certain disease-associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

TNF is also associated with yeast and fungal infections. Specifically Candida Albicans has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., Journal of Infectious Diseases, Vol. 164, p. 389-95 (1991). See also Wasan et al., Antimicrobial Agents and Chemotherapy, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., Journal of Infectious Diseases, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

Summary of the Invention

This invention comprises benzyl pyrrolidinones represented by Formula (I), and pharmaceutical compositions containing these compounds.

This invention further constitutes a method of inhibiting phosphodiesterase IV in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I). Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophillic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, (Kidney Int. 37:362, 1990; Kidney Int. 35:494, 1989) and central nervous system disorders such as depression and multi-infarct dementia.

This invention further constitutes a method of inhibiting the production of TNF in an animal, including humans, which comprises administering to an animal in need thereof, an effective amount of a compound of formula (I).

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically

administering an effective amount of a compound of Formula I.

The compounds of the present invention are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as, Herpes Zoster and Herpes Simplex.

The compounds of Formula I are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo.

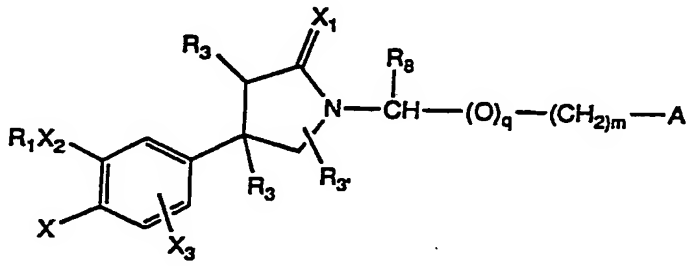
A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The preferred organism for treatment is the Candida organism. The compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Detailed Description of the Invention

The compounds of this invention are illustrated by the formula (I)



(I)

wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group; C_{4-6} cycloalkyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl, $(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_xOH$, $(CR_{14}R_{14})_sO(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_sO(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_y-R_{11}$, or $(CR_{14}R_{14})_z-R_{10}$;

X_1 is O or S;

X_2 is O or NR_{14};

X_3 is hydrogen or X;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$, or formamide;

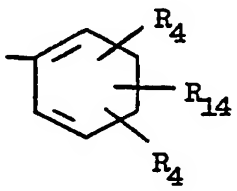
Y is O or S(O)m;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 5 fluorines;

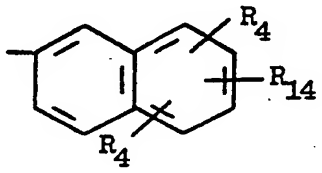
R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, OR_5, $-CH_2OR_5$, $-NR_5R_{16}$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $C(O)NR_5R_{16}$, $-CH=CR_9R_9$, $-C\equiv CR_9$ or $-C(=Z)H$;

$R_{3'}$ is hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or $-C(=Z)H$;

A is



(a)



or

(b)

(c) C_{1-3} alkyl unsubstituted or substituted by one or more fluorines or one or two R_4 groups;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

x is an integer from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

R_4 is independently hydrogen, Br, F, Cl, $-NR_5R_6$, NR_6R_{16}, NO_2, $-C(Z)R_7$, $-S(O)_mR_{12}$, CN, OR_{16}, $-OC(O)NR_5R_{16}$, 1 or 2-imidazolyl, $-C(=NR_{16})NR_5R_{16}$, $-C(=NR_5)-SR_{12}$, $-OC(O)CH_3$, $-C(=NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}-C(O)-R_{15}$, $C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl;

or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is H, R_{12}, $-C(O)R_{12}$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-S(O)_mCF_3$, $-C(=NCN)SR_{12}$, $-C(=NCN)R_{12}$, $-C(=NR_{16})R_{12}$, $-C(=NR_{16})SR_{12}$ or $-C(=NCN)NR_5R_{16}$;

R_7 is OR_5, $-NR_5R_{16}$, or R_{12};

R_8 is hydrogen, $C(O)R_7$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl-[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-,4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl);

R_9 is hydrogen, F or R_{12}.

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted aryloxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, furan, pyran, thiophene, thiopyran, C_{3-6} cycloalkyl, or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyran or 2-tetrahydro-thiopyran, 2-tetrahydrofuran or 2-tetrahydrothiophene unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is C_{1-4} alkyl unsubstituted or substituted by one or more halogens; $-C(O)C_{1-4}$ alkyl, unsubstituted or substituted by one or more halogens; oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5;

Z is O, $-NR_{12}$, $-NOR_5$, NCN, $-C(-CN)_2$, $-CR_5NO_2$, $-CR_5C(O)OR_{12}$, $-CR_5C(O)NR_5R_5$, $-C(-CN)NO_2$, $-C(-CN)C(O)OR_{12}$ or $-C(-CN)C(O)NR_5R_5$;

or a pharmaceutically acceptable salt thereof; provided that m is 2 when R_{10} is OH in $(CR_{14}R_{14})n-C(O)O-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$, or $C(R_{14}R_{14})_sO(CR_{14}R_{14})_mR_{10}$ and further provided that at least one of the R_4 or R_{14} groups on (a) or (b) is not hydrogen when q is 0, R_3, $R_{3'}$, R_8 and X_3 are H; X is OR_2, X_2 is O and X_4 is O or S.

Also included in this invention are pharmaceutically acceptable salt complexes of the compounds of this invention which can form salts.

All defined alkyl groups can be straight or branched.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention. The term "halogen" is used to mean chloro, fluoro, bromo or iodo. Alkyl groups may be substituted by one or more halogens up to being perhalogenated.

By the term "cycloalkyl" as used herein is meant to include groups of 3-6 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

Examples of C_{7-11} polycycloalkyl are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo $5.2.1.0^{2,6}$]decyl, etc. additional exmaples of which are described in Saccamano et al., WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R_5 and R_{16} in the moiety $-NR_5R_{16}$ together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazoly, 2-triazolyl, tetrazolyl, 2-tetrazoyl, morpholinyl, piperazinyl, or pyrrolyl ring.

The invention further provides for the novel pharmaceutical compositions of the compounds of Formula I.

The invention provides a method of inhibiting PDE IV which comprises administering to a subject in need thereof, a compound of Formula (I).

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

The invention also provides a method for the treatment of asthma which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

The compounds of Formula (I) are useful in treating, prophylactically or therapeutically, disease

states in humans which are exacerbated or caused by excessive or unregulated TNF production.

Therefore, the present invention also provides a method for the inhibition of the production of tumor necrosis factor (TNF) in an animal in need thereof, including humans, which comprises administering to the animal in need of such treatment an effective amount of a compound of Formula I.

By the term "inhibiting the production of TNF" is meant

a) a decrease of excessive in vivo TNF levels in a human to normal levels or below normal levels by inhibition of the in vivo release of TNF by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcription level, of excessive in vivo TNF levels in a human to normal levels or below normal levels; or

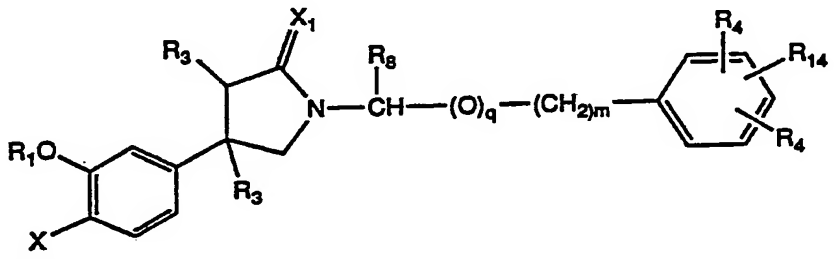
c) a down regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

By the term "TNF mediated disease states" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action is exacerbated or which is secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

By the term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte

but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and β-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNFα) and Tumor Necrosis Factor beta (TNFβ).

A preferred subgroup of formula I is formula (Ib):



(Ib)

wherein:

R_1 is C_4-C_6 cyclic alkyl, unsubstituted or substituted by one to three methyl or ethyl groups; C_{1-7} alkyl, unsubstituted or substituted by 1 to 3 fluorines; $-(CH_2)_sC(O)O-(CH_2)_mCH_3$; $-(CH_2)_sO(CH_2)_mCH_3$; $-(CH_2)_sOH$; $-CH_2$-cyclopentyl; $-CH_2$-cyclopropyl or 3-tetrahydrofuranyl;

s is 2 to 4;

m is 0 to 2;

X is $-YR_2$, halogen, nitro, amine, C_{1-2}dialkyl-amine, C_{1-2}monoalkylamine, or formyl amine;

Y is O or $S(O)_m$;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 4 fluorines;

R_3 is H, CH_3, CN, F, OH, $-C\equiv CR_9$ or CF_3;

X_1 is O or S;

q is 0 or 1;

R_4 is independently hydrogen, Br, F, Cl,

$-NR_5R_{16}$, NO_2, $-C(Z)R_7$, $-S(O)_mC_{1-3}$alkyl, CN, OR_{16}, $-OC(O)NR_5R_{16}$,1 or 2-imidazolyl, $-C(=NR_{16})NR_5R_{16}$, $-C(=NR_5)-SR_{12}$, $-C(O)R_{15}$, $-OC(O)CH_3$, $-C(=NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$ or $-NH-C(O)-R_{15}$;

R_5 is independently hydrogen or C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_6 is H, R_{12}, $-C(O)R_{12}$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$; $S(O)_mCR_{12}$, $-S(O)_mCF_3$, $-C(=NCN)SR_{12}$, $C(=NCN)NR_5R_{16}$, $-C(=NCN)R_{12}$, or $-C(=NR_{16})R_{12}$;

R_7 is OR_5, NR_5R_{16} or R_{12};

R_8 is H or $-C(O)R_7$;

R_9 is hydrogen, F or R_{12};

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is H or a C_{1-2}alkyl unsubstituted or substituted by one or more fluorines;

R_{15} is C_{1-4} alkyl unsubstituted or substituted by one or more halogens; $-C(O)C_{1-4}$ alkyl, unsubstituted or substituted by one or more halogens; oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morphollinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5; or a pharmaceutically acceptable salt thereof;

Preferred compounds are those in which R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, tetrahydrofuran, cyclopentenyl, $-C_{1-7}$ alkyl optionally substituted by one or more fluorines or chlorines and $-(CH_2)_{2-4}OH$; X_1 and X_2 are oxygen, X is YR_2 and Y is oxygen; R_2 is a C_{1-2} alkyl optionally substituted by one or more halogens, preferably fluorine or chlorine; one R_3 is hydrogen and the other R_3 is hydrogen, $C\equiv CR_9$, CN, $C(=Z)H$, CH_2OH, CH_2F, CF_2H, or CF_3; Z is O, NCN or NOR_5; $R_{3'}$ is hydrogen; X_3 is hydrogen; A is (a); R_4 is H, Br,

OR_{16}, CN, NR_5R_6, NO_2, $C(O)R_7$, $S(O)_mR_{12}$, 1- or 2-imidazolyl, $-OC(O)CH_3$ or $NHC(O)R_{15}$; R_8 is C(O)OH, H or C(O)OEt; R_{14} is hydrogen, CH_3, NH_2 or $NHC(O)CH_3$.

More preferred are compounds in which R_1 is C_{1-4} alkyl substituted by 1 or more fluorines, CH_2-cyclopropyl, CH_2-cyclopentyl, cyclopentyl or cyclopentenyl; R_2 is methyl or fluoro substituted C_{1-2} alkyl; R_3 is hydrogen, C≡CH or CN; and R_4 is hydrogen, Br, NH_2, $-NHC(O)CH_3$, C(O)OH, $-NHC(NCN)SCH_3$, $-NHC(O)NH_2$, $-N(CH_3)_2$, $NHC(O)C(O)OCH_3$, $-NHC(O)C(O)OH$, $-NHS(O)_2CH_3$, $-C(O)OCH_3$, $S(O)_2CH_3$, SCH_3, $-NHC(O)C(O)CH_3$, $S(O)CH_3$, $-NHC(O)C(O)NH_2$, CN, $C(O)NH_2$, $NHS(O)_2CF_3$, $C(NH)NH_2$, $O-C(O)CH_3$, $-C(O)N(CH_3)_2$, 1- or 2-imidazolyl, $-NHC(O)CH_2Cl$, -NHC(O)-oxazolidinyl, -NHC(O)-4,4-dimethyl-oxazolidinyl or OH.

Most preferred are compounds wherein R_1 is cyclopentyl, CF_3, CH_2F, CHF_2, CF_2CHF_2, CH_2CF_3, CH_2CHF_2, CH_3, CH_2-cyclopentyl, CH_2-cyclopropyl or cyclopentenyl; R_2 is CF_3, CHF_2, or CH_2CHF_2; one R_3 is hydrogen and the other R_3 is hydrogen, C≡CH or CN and is in the 4-position; one R_4 is hydrogen and the other is $NHC(O)CH_3$, NH_2, $NH-C(=NCN)SCH_3$, $NHC(O)CO_2CH_3$, $C(O)OCH_3$, $NHC(O)NH_2$, $NHC(O)C(O)CH_3$, or $NHC(O)C(O)NH_2$; or wherein both R_4 groups are NH_2 or $NHC(O)CH_3$; R_8 is hydrogen and R_{14} is hydrogen.

Especially preferred are the following compounds:

1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

1-(4-Oxamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diacetamidobenzyl)-2-pyrrolidinone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diaminobenzyl)-2-pyrrolidinone;

1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone;

1-(4-N-Carbomethoxycarbamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

4-(3-(Cyclopentyloxy-4-methoxyphenyl)-1-(4-N-[ureido]benzyl-2-pyrrolidone; and

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-pyruvamidobenzyl)-2-pyrrolidinone.

Most especially preferred are:

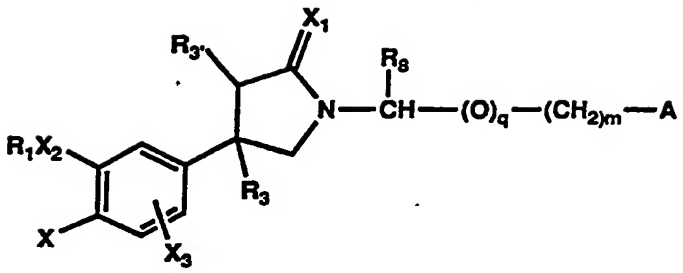
(S)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(S)-1-4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

General Synthesis

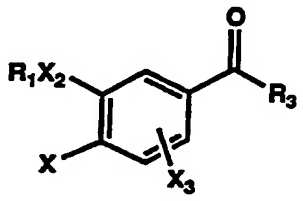
Compounds of the Formula (Ia)



(Ia)

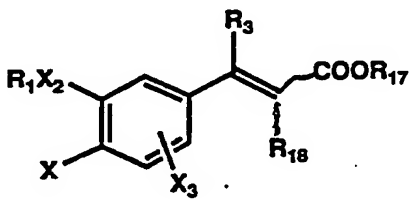
can be prepared by a process which comprises:

a) for compounds wherein R3 is H, R12 or cyclopropyl unsubstituted or substituted by R9 and X and X3 are other than $S(O)_mR_2$ (wherein m = 1 or 2), Br, I, NO_2 or formyl amine; reacting a compound of the Formula (2)



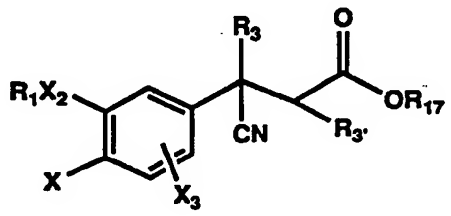
(2)

wherein X_2R_1, X and X3 respectively represent X_2R_1, X and X3 as defined in relation to Formula (I) or groups convertable to X_2R_1, X and X3; and X_1 is H, with an appropriate malonic acid ester derivative, such as dimethyl malonate, in a suitable solvent, such as benzene or toluene, at reflux with or without an appropriate catalyst (e.g., titanium tetrachloride or a tertiary amine base with or without added acid) and/or with azeotropic removal of water under an inert atmosphere, to provide a compound of Formula (3) wherein R_{17} is an alkyl or aryl group and R_{18} is $COOR_{17}$;



(3)

Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetra-alkylammonium cyanide, provides compounds of the Formula (4)

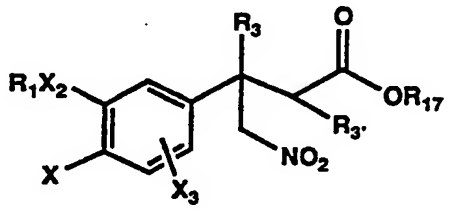


(4)

wherein R3' is H or $COOR_{17}$, typically as a mixture.

Alternatively, reaction of a compound of the Formula (2) with, e.g., carboalkoxy- or carboaryloxy-methylene trialkyl- or triarylphosphorane, provides a compound of the Formula (3) wherein R_{18} is H. Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetra-alkylammonium cyanide, also provides compounds of the Formula (4) wherein R3' is H.

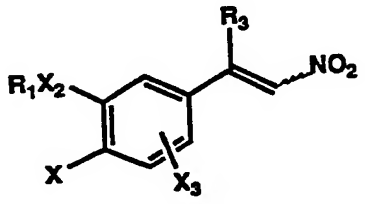
Alternatively, reaction of a compound of the Formula (3) wherein R_{18} is H with the anion of nitromethane generated from an appropriate base or in the presence of an appropriate catalyst, such as alkoxide, a tetraalkylguanidine or a quaternary ammonium halide, in an appropriate solvent, such as an alcohol or nitromethane, provides an ester compound of the Formula (5)



(5)

wherein $R_{3'}$ is $COOR_{17}$, which may be hydrolyzed and decarboxylated to provide a compound of the Formula (5) wherein $R_{3'}$ is H. Similarly, compounds of the Formula (5) wherein $R_{3'}$ is H, may be derived from first,

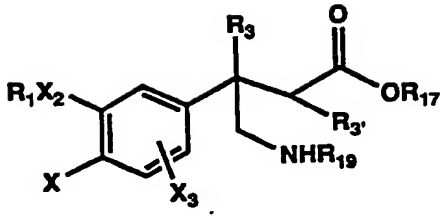
1) reaction of a compound of the Formula (2) with nitromethane as described above to provide a compound of the Formula (6)



(6)

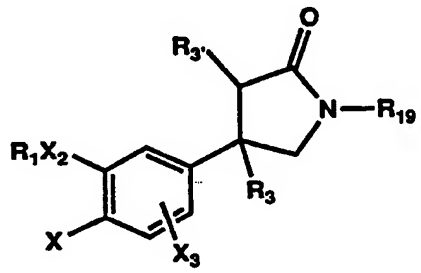
followed by 2) further reaction of a such a compound of the Formula (6) with an alkyl or aryl acetate anion, generated at an appropriate temperature (e.g., -78°C) in an appropriate solvent (e.g., tetrahydrofuran) using an appropriate base (e.g., lithium diisopropylamide or lithium hexamethyldisilazide).

Alternatively, reaction of a compound of the Formula (9) (as described below) wherein R_{20} is H and R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9 with a strong base, followed by reaction with an appropriate alkyl or aryl α-halo carboxylate, such as methyl α-bromoacetate, will also provide a compound of the Formula (4) wherein R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9. Reduction of the nitrile group of such compounds of the above Formula (4) or of the nitro group of the above similar compounds of the Formula (5) provides compounds of Formula (7)



(7)

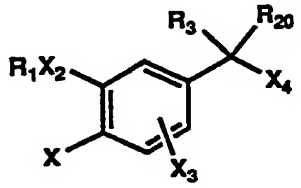
wherein R_{19} is H. Reaction of amines of the Formula (7) wherein R_{19} is H with an aldehyde in a suitable solvent, such as chloroform at reflux temperature, followed by reduction of the imine with, for example, sodium cyanoborohydride in the presence of an acid in methanol, provides compounds of the Formula (7) wherein R_{19} is $CH_2(CH_2)_mA$; cyclization of such compounds of the Formula (7) then provides the corresponding compounds of Formula (Ia). Alternatively, treatment of compounds of Formula (7) wherein R_{19} is H with or without a catalyst in an appropriate solvent with an appropriate activated alkylating agent, such as a halide, mesylate or tosylate, provides compounds of the Formula (7) wherein R_{19} is $CHR_8(O)_q(CH_2)_mA$, which may be cyclized as above to the corresponding compounds of Formula (Ia). In addition, cyclization of above compounds of the Formula (7) wherein R_{19} is H provides compounds of the Formula (8)



(8)

wherein R_{19} is H; reaction of appropriate compounds of the Formula (8) wherein R_{19} is H with a strong base, such as sodium hydride, followed by reaction of the generated amide anion with an appropriate activated alkylating agent, such as a halide, mesylate or tosylate, also provides the compounds of the Formula (Ia).

b) for compounds wherein R3 is CN and X and X3 are other than S(O)mR2 (wherein m = 1 or 2), Br, I, NO2 or formyl amine, a sequence beginning with reaction of a compound of the Formula (2) wherein R3 is H with a lithium halide and a silyl halide in an appropriate solvent followed by reduction with an appropriate reductant, such as a siloxane, provides compounds of the Formula (9)



(9)

wherein X4 is chloro or bromo and R3 and R20 are H; alternatively, reduction of a compound of the Formula (2) wherein R3 is H with e.g., sodium borohydride in methanol, provides compounds of the Formula (9) wherein X4 is OH and R3 and R20 are H, which is reacted with, e.g., phosphorous trichloride, thionyl chloride, phosphorus tribromide, cupric bromide or carbon tetrabromide with triphenyl phosphine, to also provide compounds of the Formula (9) wherein X4 is chloro or bromo and R3 and R20 are H. Halide displacement by cyanide then provides compounds of the Formula (9) wherein X4 is CN and R3 and R20 are H, which is allowed to react with a strong base, such as a butyl lithium, at reduced temperature under an inert atmosphere and then may be a) treated with, e.g., anhydrous magnesium bromide, and then reacted with, for example, trimethylsilyl isocyanate and appropriate workup, to produce compounds of Formula (9) wherein R3 is CONH2, R20 is H and X4 is CN or b) reacted with, for example, an alkyl or aryl haloformate, such as methyl chloroformate, to produce compounds of the Formula (9)

wherein R_3 is $COOR_{17}$, R_{20} is H and X_4 is CN; the $COOR_{17}$ group of such a compound may be transformed either at this or a later stage to a $CONH_2$ group by any of the standard techniques known in the art, such as reaction with concentrated ammonium hydroxide.

Alternatively, a compound of the Formula (9) wherein R_3 is $COOR_{17}$, R_{20} is H and X_4 is CN may also be obtained by reaction of a compound of the Formula (9) wherein R_3 and R_{20} are H and X_4 is CN with a metal hydride, such as sodium hydride, in the presence of a dialkyl or diaryl carbonate, such as dimethyl carbonate. Also, such compounds may be obtained by homologation of a compound of the Formula (2) wherein R_3 is H to a compound of the Formula (9) wherein R_3 is $COOR_{17}$ and X_4 and R_{20} are H by any number of known processes, such as reaction with methyl methylsulfinylmethyl sulfide and a base, e.g., sodium hydroxide, followed by treatment with, e.g., alcoholic acid. Generation of an anion of such compounds of the Formula (9) with a suitable base, followed by reaction with, e.g., cyanogen chloride or 2-chlorobenzyl thiocyanate, provides compounds of the Formula (9) wherein R_3 is $COOR_{17}$, R_{20} is H and X_4 is CN. Generation of an anion from compounds of the Formula (9) wherein R_{20} is H, X_4 is CN and R_3 is $CONH_2$ or $COOR_{17}$ with the appropriate base in an appropriate solvent followed by reaction with an alkyl or aryl α-halo carboxylate provides a compound of Formula (4) wherein R_3 is $CONH_2$ or $COOR_{17}$; reduction of the nitrile moiety of such compounds by, for example, hydrogenation with a noble metal or Raney nickel catalyst, provides compounds of the Formula (7) wherein R_{19} is H and R_3 is $CONH_2$ or $COOR_{17}$. The amine moiety of compounds of the Formula (7) wherein R_{19} is H and R_3 is $CONH_2$ is then protected to provide a compound of the Formula (7) wherein R_{19} is a protecting group, such as a t-butyloxycarbonyl group, and R_3 is $CONH_2$; amide dehydration with, for example, trifluoroacetic anhydride, followed by protecting group

removal then provides compounds of the Formula (7) wherein R_{19} is H and R_3 is CN, which may then be transformed as described above for other compounds of the Formula (7) to the compounds of the Formula (Ia) wherein R_3 is CN and X and X_3 are other than $S(O)_mR_2$ (wherein m = 1 or 2), Br, I, NO_2 or formyl amine.

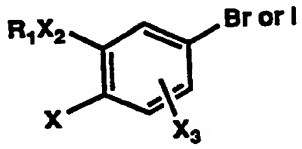
c) compounds wherein R_3 of Formula (I) is OR_5 or F and X and X_3 are other than $S(O)_mR_2$ (wherein m = 1 or 2), Br, I, NO_2 or formyl amine are prepared employing a sequence beginning with a cyanohydrin with the hydroxyl suitably protected as a silyl ether, an acetal, or an ester such as a t-BOC. Treatment of a compound of the Formula (2) wherein R_3 is is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9 with, for example, a derivative of hydrocyanic acid provides the cyanohydrins of Formula (9) wherein R_3 is H, R_{20} is OH and X_4 is CN. Subsequent treatment of the Formula (9) compounds with a suitable protecting agent such as trimethylsilyl chloride, di-t-butyldicarbonate and a suitable base, or methyl vinyl ether or direct treatment of the Formula (2) compound with trimethylsilylcyanide and a Lewis Acid provides the protected cyanohydrin of Formula (9) in which R_3 is H, R_{20} is the protected hydroxyl and X_4 is CN. The protected cyanohydrin is treated with a strong hindered base, such as LDA, at reduced temperature under an inert atmosphere followed by reaction with, e.g., a bromoacetic acid ester and appropriate workup to produce a compound of Formula (4) wherein R_3 is the protected hydroxyl and R_3' is H. Reduction of the nitrile moiety of such compounds by, for example, hydrogenation with Raney nickel catalyst, provides Formula (7) compounds wherein R_{19} is H and R_3 is the protected or unprotected hydroxyl. These Formula (7) compounds may be alkylated on nitrogen and cyclized as described above,then treated with diethylaminosulfur trifluoride to provide the Formula (Ia) compounds wherein R_3 is F.

d) compounds of Formula (Ia) wherein R3 represents the remaining R3 groups of Formula (Ia) may be derived from the compounds of the Formulas (8) or (Ia) wherein R3 is CN by protection of the amide and other sensitive functionality, and manipulation of the CN function as, for example, reduction of the R3 CN moiety to CHO and functional group transformation of the CHO by any of the standard conditions well known in the art.

Some compounds of Formula (Ia) are prepared from other compounds of Formula (Ia) by appropriate manipulation of functional groups present in or as the A, X, X_1, X_2R_1, R3 or R3' moieties.

Compounds of Formula (Ia) wherein R3 is CF_3, CHF_2 or CH_2F may be prepared from the corresponding Formula (2) compounds using the methods described above. The formula (2) compounds where R3 is CF_3 are obtained by the method of Shono et al., J. Org. Chem., Vol. 56, pages 204 (1991) electrochemically from the Formula (2) compounds where R3 is H.

Formula (2) compounds where R3 is CF_3 or CF_2H are obtained by treatment of compounds of the Formula (10)



(10)

with a metalling agent at -78°C followed by trifluoroacetic acid or difluoroacetic acid by the method of Nad et al., Izvest, (1959) page 71; Chem. Abstr. vol. 53, No. 14977; and Vol. 53, No. 17933 (1959).

Formula (2) compounds where R3 is CH_2F are obtained by treatment of the Formula (2) compounds where

R_3 is CH_3 according to the method of Rozen et al., Synthesis (6)665, (1985).

For compounds wherein X is $S(O)_mR_{12}$, and m is 1 or 2 the final compound is made from the $-SR_{12}$ moiety by oxidizing the intermediate $-SR_{12}$ product under conditions well known to those skilled in the art, after the appropriate $CONH_2$ moiety in the synthetic sequence is dehydrated to the cyano moiety. For compounds where X and/or X_3 are Br, I, nitro, amine or formyl amine, synthesis of these compounds is accomplished by any of the steps described above using a suitably protected amine as X and/or X_3. Such protecting groups are known to those skilled in the art and are readily disclosed in Greene, T., Protective Groups in Organic Synthesis, Wiley Publishers, NY (1981), the contents of which are hereby incorporated by reference. The deprotected amine is then appropriately acylated to the formyl amine moiety, oxidized to the NO_2 moiety, or diazotized and displaced by methods well known to those skilled in the art to produce the desired Br or I moiety.

With appropriate manipulation and protection of any chemical functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (I) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, sublingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (I) and their pharmaceutically acceptable salts which are active when

given orally can be formulated as syrups tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or

other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg to 100 mg/Kg, and preferably from 0.01 mg to 30 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 40 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable salt therof calculated as the free base. Each dosage unit for intranasal administration or oral inhalation contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 001 to 1.0% of a compound of formula (I). Each dosage unit for rectal administration contains suitably 0.01 mg to 100 mg of a compound of formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably abut 0.001 mg/Kg to 40 mg/Kg, for example abut 0.001 mg/Kg to 40 mg/Kg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 1200 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit antiinflammatory activity, or if used as a TNF inhibitor, the active

ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

The biological activity of the compounds of formula I as in PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula I on PDE IV

I. Isolation of PDE Isozymes

Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (Torphy et al., J. Biol. Chem., 267: 1798-1804 (1992)).

TABLE 1. Characteristics of PDE isozymes.[a]

Peak	Isozyme	K_m (mM)	
		cAMP	cGMP
1a	cGMP-specific	135	4
Ib	Ca^{2+}/calmodulin-stimulated	50	5
Ic	Ca^{2+}/calmodulin-stimulated	1	2
III	cGMP-inhibited	0.4	8
IV	Ro 20-1724-inhibited	4	38

[a] Data are from Torphy and Cieslinski, supra.
[b] Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22:1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990. IC_{50}s for compounds of this invention range from 25 nM to 500 μM..

III. cAMP Accumulation in U-937 Cells

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-100 μM) of PDE inhibitors for one minute and 1 μM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A

general protocol for this assay is described in Brooker et al., Radioimmunassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. Data are expressed as both an EC_{50} for increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC_{50}s for compounds of this invention range from 0.030 μM to >10 μM.

Inhibitory Effect of Compounds of Formula (I) on TNF Production

I. Inhibitory Effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes

The inhibitory effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes may be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

II. In vivo actity

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The following examples are illustrative, and not limiting of the compounds of this invention.

EXAMPLE 1

R-(+)- and S-(-)-1-(4-Bromobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) 3-Cyclopentyloxy-4-methoxybenzaldehyde A mixture of 3-hydroxy-4-methoxy-benzaldehyde (40 g, 0.26 mol), potassium carbonate (40 g, 0.29 mol) and bromocyclopentane (32 mL, 0.31 mol) in dimethylformamide (0.25 L) was heated under an argon atmosphere at 100°C. After 4 h, additional bromocyclopentane (8 mL, 0.08 mol) was added and heating was continued for 4 h. The mixture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure and the residue was partitioned between ether and aqueous sodium carbonate. The organic extract was washed with aqueous sodium carbonate and dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 2:1 hexanes/ether to provide a pale yellow oil of 3-cyclopentyloxy-4-methoxybenzaldehyde (52 g, 89%). Analysis Calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.71, H 7.33.

b) Dimethyl (3-cyclopentyloxy-4-methoxybenzylidene)-malonate A mixture of 3-cyclopentyloxy-4-methoxybenzaldehyde (22.3 g, 101 mmol), dimethylmalonate (17 mL, 101 mmol), piperdine (0.5 mL, 0.861 mmol), and acetic acid (0.3 mL, 0.861 mmol) in a solution of benzene (50 mL0 under an argon atmosphere was stirred at reflux with azeotropic removal of water. After six hours, the solvent was removed *in vacuo*, the residue was partitioned between ether and saturated sodium carbonate and extracted. The organic extracts were dried (potassium carbonate) and concentrated to provide an orange oil of the title compound (33.5 g, 100%), which as used without further purification.

c) Methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-propionate Dimethyl (3-cyclopentyloxy-4-methoxybenzylidene)-malonate (33.5 g, 101 mmol) was dissolved in methanol (250 mL) and was treated with potassium cyanide (6.7 g, 101 mmol) in water (5 mL0. The mixture was heated to reflux. After five hours, the solvent was removed *in vacuo*, the residue was partitioned between ether and sodium bicarbonate (5%) and extracted three times. The organic extracts were dried (potassium carbonate) and the solvent was removed *in vacuo*. The residual oil was purified by flash chromatography eluting with 25-40% ethyl acetate/hexanes to provide a white solid of the title compound (13.2 g, 43%).

d) Methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)-butyrate Methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate (6.0 g, 19.8 mmol) and 70% perchloric acid (1.95 mL) were added to a suspension of 10% palladium on carbon (0.9 g) in methanol (100 mL). The mixture was hydrogenated at 50 psi for 1.5 h, diluted with methylene chloride, filtered through celite and evaporated. The residue was partitioned between methylene chloride and dilute aqueous sodium bicarbonate and extracted three times. The organic layer was dried (potassium carbonate). Solvent evaporation provided the amine (6.0 g, 100%) as a yellow oil.

e) 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone
A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (6.0 g, 19.8 mmol) in toluene (100 mL) and a catalytic amount of sodium cyanide were refluxed for 20 hours. The solvent was removed *in vacuo* to yield a residue which was partitioned between methylene chloride and water and extracted two times.

The organic layer was dried (potassium carbonate) and evaporated to a solid. Purification by flash chromatography, eluting with 95:5 chloroform/methanol to provided a solid (3.7 g, 67%): m.p. 130 °C.

f) R-(+)-and S-(-)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone Chiral separation of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone was accomplished using preparative HPLC conditions with a 8 cm x 55 cm column packed with 1.0 kg E. Merck cellulose triacetate (15-25 m). The mobile phase of 95:5 ethanol/water eluted at a flow rate of 20 mL/min with injection of 1 g/30 mL at ambient temperature. Ultraviolet detection of the eluting product was employed at 254 nm. Retention times were 68 min for the S-(+) isomer and 86 min for the R-(-) isomer, with recovery of 88% (>99% ee) and 87% (>98% ee), respectively.

g) R-(+)- and S-(-)-1-(4-Bromobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)2-pyrrolidinone In a separation reaction, a solution of chiral 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (510 mg, 1.85 mmol) in dry dimethylformamide (10 mL) under an argon atmosphere was treated with sodium hydride (62 mg of 80% dispersion, 2.04 mmol) at room temperature for 45 minutes. To the mixture, p-bromobenzylbromide (509 mg/ 2.04 mmol) was added in a solution of dimethylformamide (1 mL) and stirred for three hours. Water was added and the mixture was extract three times with ether. The combined extracts were dried (potassium carbonate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 9:1 ether/methylene chloridere to provide a solid of the title compound (630 mg, 76.5%): m.p. 100-102°C.

Analysis Calc. for $C_{23}H_{26}NO_3Br$: C 62.17, H 5.90, N 3.15, Br 17.98; found: R-(=) C 62.01, H 5.88, N 3.16; S-(-) C 62.14, H 5.96, N 3.16, Br 18.21.

$[a]_D^{25}$ (cl, methanol) = +50.4°C

$[a]_D^{25}$ (cl, methanol) = -48.1°C

EXAMPLE 2

1-(Benzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (689 mg, 2.5 mmol) was added to a suspension of sodium hydride (90 mg, 3.0 mmol of an 80% dispersion, washed 3 times with hexanes) in dry dimethylformamide (12 mL), and stirred under an argon atmosphere. After 2.5 h, benzyl bromide (360 mL, 3.03 mmol) was added and the reaction mixture was stirred at room temperature for 16 hours. Water was added to the reaction mixture and it was extracted with methylene chloride. The organic extract was dried (potassium carbonate) and concentrated. Purification by flash chromatography, eluting with 9:1 ether/methylene chloride provided a pale yellow oil of the title compound (548 mg, 60.0%).

Analysis Calc. for $C_{23}H_{27}NO_3 \cdot 1/2H_2O$: C 73.77, H 7.54, N 3.74; found: C 73.52, H 7.18, N 3.72.

EXAMPLE 3

1-(4-Carboxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

1-(4-Carboxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone (200 mg, 0.73 mmol)

prepared as in Example 1 was added to a suspension of sodium hydride (90 mg of an 80% dispersion, 3 mmol) in dry dimethylformamide (5 mL) containing 15-crown-5 ether (100 mL). The suspension was stirred under an argon atmosphere at room temperature until gas evolution slowed, and then it was heated at 50°C for 5 minutes to provide a solution of the sodium salt. In a separate flask, chloromethylbenzoic acid (183 mg, 1.08 mmol) was dissolved in dry tetrahydrofuran (3 mL) and cooled to -78°C. n-Butyllithium (440 mL of a 2.5 N solution, 1.08 mmol) was added dropwise to the acid and the solution was allowed to warm to 0°C. The solution of the sodium salt was added slowly to the lithium salt of the acid and the mixture was allowed to warm to room temperature. The resulting solution was poured into ice water, acidified with 3M hydrochloric acid and extracted with methylene chloride. The organic extracts were washed two times with water and dried (sodium sulfate). The residue was purified by flash chromatography eluting with, 1:1 ether/methylene chloride containing 1% acetic acid. The title compound (94 mg, 32%), a solid, was recrystallized from ethanol/ether: m.p. 173.5-175.5°C. Analysis Calc. for $C_{24}H_{27}NO_5$: C 70.40, H 6.65, N 3.42; found: C 70.26, H 7.63, N 3.40.

EXAMPLE 4

S-(-)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) S-(-)-1-(4-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone S-(+)-4(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (1.8 g, 6.5 mmol) prepared as in Example 1 was added to a suspension of sodium hydride (196 mg, 6.53 mmol of an 80% dispersion) in dry dimethylformamide (65 mL) containing 15-crown-5 ether (1.28 mL). The suspension was stirred under an argon atmosphere overnight at room

temperature, and then heated at 50-60°C for 90 minutes to provide a solution of the sodium salt. 4-Nitrobenzylbromide (2.79 g, 12.9 mmol) wad dissolved in dry tetrahydrofuran (70 mL) and the solution of the sodium salt was added. The reaction mixture was stirred overnight and the tetrahydrofuran was removed *in vacuo*. The resulting solution was poured into ice water, acidified with 3M hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed six times with water, dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by two flash chromatographies, first eluting with 1-2% methanol/chloroform then eluting with 3:1 ethyl acetate/hexanes to provide a yellow resin of the title compound (505 mg, 19%).
$[a]_D^{25}$(0.61, methanol) = -48.5°C.

b) <u>S-(-)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone</u> A solution of S-(-)-1-(4-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (450 mg, 1.1 mmol) in anhydrous tetrahydrofuran (9mL) was treated with ammonium formate (1.04 g, 16.4 mmol) and 10% palladium on carbon (127 mg) in a suspension of methanol (25 mL). The suspension was stirred for three hours. The reaction was then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water. After extracting, the organic layer was washed two time with water, dried (potassium carbonate) and concentrated *in vacuo*. The resin was purified by flash chromatography eluting with a gradient of 50-75% ethyl acetate/methylene chloride to provide a colorless resin of the title compound (342 mg, 81%).

Analysis Calc. for $C_{23}H_{28}N_2O_3 \cdot 1/5H_2O$: C 71.92, H 7.45, N 7.29; found: C 71.97, H 7.60, N 7.28

$[a]_D^{25}$(0.63, methanol) = -72.5°.

EXAMPLE 5

R-(+)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, sb 201158

R-(+)-1-(4-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone R-(-)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (1.81 mg, 6.57 mmol) prepared as in Example 1 was added to a suspension of sodium hydride (202 mg of an 80% dispersion) in dry dimethylformamide (65 mL) containing 15-crown-5 ether (1.28 mL). The suspension was stirred under an argon atmosphere overnight at room temperature, and then heated at 50-60°C for 90 minutes to provide a solution of the sodium salt. 4-Nitrobenzylbromide (2.79 g, 12.9 mmol) was dissolved in dry tetrahydrofuran (70 mL) and the solution of the sodium salt was added. The reaction mixture was stirred overnight and the tetrahydrofuran was removed *in vacuo*. The resulting solution was poured into ice water, acidified with 3M hydrochloric acid and extracted with ethyl acetate. The organic extracts were washed six times with water, dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by flash chromatography, eluting with 1-3% methanol/chloroform to provide a yellow resin (570 mg, 21%).

$[a]_D^{25}$(0.63, methanol) = +43.8°.

R-(+)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of R-(+)-1-4-(4-nitrobenzylamino)-3-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (503 mg, 1.23 mmol) in

anhydrous tetrahydrofuran (6 mL) was treated with ammonium formate (1.2 g, 19 mmol) and 10% palladium on carbon (120 mg) in a suspension of methanol (18 ml). The suspension was stirred for two hours under argon. The reaction was filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was treated with cold water and extracted twice with methylene chloride. The organic layer was washed two times with water, dried (potassium carbonate) and concentrated *in vacuo*. The resin was purified by flash chromatography, eluting with a gradient of 50-100% ethyl acetate/methylene chloride to provide a colorless oil of the title compound (396 mg, 82%).

Analysis Calc. for $C_{23}H_{28}N_2O_3 \cdot 1/5H_2O$: C 71.92, H 7.45, N 7.29; found: C 71.99, H 7.54, N 7.31.

$[a]_D^{25}$ (0.56, methanol) = +72.5°.

EXAMPLE 6

1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (650 mg, 2.12 mmol) and 4-acetamidobenzaldehyde (346 mg, 2.12 mmol) in chloroform (35 mL) under an argon atmosphere was heated at reflux for 30 min. Ten mL of the chloroform were distilled off and replaced with fresh solvent. This process was repeated after refluxing for an additional hour. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 1.6 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and a solution of sodium cyanoborohydride (200 mg, 3.2 mmol) in methanol was added. The mixture was stirred at room temperature for 2 h, partitioned between 10% ethyl acetate/ether and

ice cold 5% sodium hydroxide and the organic layer dried (sodium sulfate). The solvent was removed *in vacuo*, the residue was partitioned between ethyl acetate and water and extracted two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 0-1% methanol/ethyl acetate, and crystallization from ethyl acetate/ethyl ether provided an off white solid of the title compound (415 mg, 46%): m.p. 116-118°C.

Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/8H_2O$: C 70.69, H 7.18, N 6.59; found: C 70.52, H 6.95, N 6.53.

EXAMPLE 7

S-(-)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of S-(-)-1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as in Example 4 (77 mg, 0.2 mmol) in dry pyridine (3 mL) at 0°C was treated dropwise with acetic anhydride (90 mL, 095 mmol). The reaction was stirred overnight under an argon atmosphere and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with cold hydrochloric acid, water, 5% aqueous sodium bicarbonate and again with water. The organic layer was dried (sodium sulfate) and evaporated *in vacuo* to yield a residue which was purified by flash chromatography, eluting with a gradient of 0-2% methanol/ethyl acetate to provide a resin of the title compound (85.5 mg, 100%).

Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/H_2O$: C 70.32, H 7.20, N 6.56; found: C 70.14, H 7.22, N 6.51.

$[a]_D^{25}$ (0.49, methanol) = -56.8°C.

EXAMPLE 8

R-(+)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of R-(+)-1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as in Example 5 (115 mg, 0.3 mmol) in dry pyridine (3 mL) at 0°C was treated dropwise with acetic anhydride (125 mL, 1.3 mmol). The reaction was stirred overnight under an argon atmosphere and the solvent removed *in vacuo* to yield a residue, which was purified by flash chromatography eluting with a gradient of 0-2% methanol/ethyl acetate to provide a resin of the title compound (59.5 mg, 47%).

Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/4H_2O$: C 70.32, H 7.20, N 6.56; found: C 70.28, H 7.17, N 6.44

$[a]_D^{25}$ (0.46, methanol) = +56.9°C.

EXAMPLE 9

1-[4-N-(N'-Cyano-S-methyl-isothioureido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (219 mg, 0.59 mmol) and dimethyl N-cyanodithioiminocarbonate (90%, 194 mg, 1.19 mmol) in pyridine (2.5 mL) under an argon atmosphere was heated at reflux for 3 h. The mixture was cooled, the solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting the title compound with 40-75% ethyl acetate/methylene chloride, to provide a pale yellow oil (139 mg, 49%).

Analysis Calc for $C_{26}H_{30}N_4O_3S \cdot 1/2H_2O$: C 64.04, H 6.41, N 11.49, S 6.57; found: C 64.09, H 6.39, N 11.15, S 6.57.

EXAMPLE 10

1-[4-N-(N'-Cyanoguanidino)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-[4-N-(N'-cyano-S-methyl-isothioureido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (100 mg, 0.21 mmol) in ethanol under an argon atmosphere was saturated with ammonia and heated at 95°C for 24 h. The mixture was cooled, the solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting the title compound with 5% isopropanol/methylene chloride and adding 0-5% methanol to provide a glass like solid of the title compound (48.5 mg, 51.7%).

Analysis Calc. for $C_{25}H_{29}N_5O_3 \cdot 1/2CDCl_3$: C 62.39, H 5.99, N 14.36; found: C 62.48, H 6.06, N 14.26.

EXAMPLE 11

1-[4-N-(ureido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (350 mg, 1.05 mmol) in aqueous acetic acid (1:1 glacial acetic acid/water) under an argon atmosphere was treated dropwise with an aqueous solution of sodium cyanate (223 mg, 3.4 mmol in 4 mL water). After stirring at room temperature for 30 min, the reaction was poured into ice-water and extracted with methylene chloride, washed three times with water and dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 80% ethyl acetate/methylene chloride containing 7-10% methanol to provide a solid of the title compound which was recrystallized from methylene chloride/ether (258 mg, 58%): m.p. 113-115.5°C.

Analysis Calc. for $C_{24}H_{29}N_3O_4$: C 68.06, H 6.90, N 9.92; found: C 67.70, H 6.89, N 9.95

EXAMPLE 12

1-(4-Dimethylaminobenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinone

a) A mixture of 3,4-dimethoxybenzaldehyde (20.0 g, 120 mmol), dimethylmalonate (16.4 g, 120 mmol), piperdine (0.3 mL, 0.517 mmol), and acetic acid (3.0 mL, 0.861 mmol) in a solution of toluene (100 mL) under an argon atmosphere was stirred at reflux with azeotropic removal of water. After two hours at reflux and overnight at room temperature, cyclohexane was added, the mixture chilled to 5°C and filtered. Recrystallization from chloroform/hexanes provided a solid (11.9 g, 35%), which was used without further purification.

b) Methyl 3-cyano-3-(3,4-dimethoxyphenyl)propionate Dimethyl (3,4-dimethoxybenzylidene)malonate (11.7 g, 42 mmol) was dissolved in methanol (70 mL) and was treated with potassium cyanide (2.7 g, 42 mmol) and water (10 mL). The mixture was stirred under argon for 18 h. The solvent was removed *in vacuo*, the residue was partitioned between ether and sodium bicarbonate (5%) and extracted with ethyl acetate six times. The organic extracts were dried (sodium sulfate) and the solvent was removed *in vacuo* to provide a yellow oil (3 g, 29%).

c) Methyl 4-amino-3-(3,4-dimethoxyphenyl)butyrate Methyl 3-cyano-3-(3,4-dimethoxyphenyl)propionate (3.0 g, 12 mmol) and 70% perchloric acid (1.9 g) were added to a suspension of 10% palladium on carbon (0.6 g) in methanol (100 mL). The mixture was hydrogenated at 50 psi for 1.25 h, diluted with methylene chloride, filtered through celite, and evaporated. The residue was partitioned between methylene chloride and dilute

aqueous sodium bicarbonate with sodium carbonate added to adjust pH above 9. The aqueous phase was extracted three times with methylene chloride and the combined organic phase was dried (potassium carbonate). Solvent evaporation provided the amine (3.0 g, 100%), a yellow oil.

d) 1-(4-Dimethylaminobenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-(3,4-dimethoxyphenyl)butyrate (1.0 g, 4.0 mmol) and 4-dimethylaminobenzaldehyde (0.6 g, 4.0 mmol) in chloroform under an argon atmosphere was heated at reflux, distilling off almost all of the solvent. Additional chloroform was added and refluxed again, distilling off most of the solvent. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid n ether (1.0 M, 4.0 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled on an ice bath and a solution of sodium cyanoborohydride (0.5 g, 8.0 mmol) was added. The mixture was stirred at zero degrees for 1 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between 25% ethyl acetate/ether and dilute, cold sodium hydroxide. The aqueous layer was extracted, the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed *in vacuo*, and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed for 7 h. The solvent was removed *in vacuo* the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 75-100% ethyl acetate/hexanes, provided a resin of the title compound (572 mg, 40%).

Analysis Calc. for $C_{21}H_{26}N_2O_3 \cdot 1/3H_2O$: C 69.98, H 7.46, N 7.77; found: C 70.08, H 7.34, N 7.72.

EXAMPLE 13

1-(4-Acetamidobenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3,4-dimethoxyphenylbutyrate (1.01 g, 4.0 mmol) and 4-acetamido-benzaldehyde (0.65 g, 4.0 mmol) in chloroform under an argon atmosphere was heated at reflux for 2.5 hours. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 4.1 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and sodium cyanoborohydride (0.50 g, 8.0 mmol) was added. The mixture was stirred at zero degrees for 1 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between 10% ethyl acetate/ether and dilute, cold sodium hydroxide. The aqueous layer was extracted, the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed for 6 h. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with a gradient of 0.5-8% methanol in 1:1 ethyl acetate/chloroform, provided a solid of the title compound which was recrystallized from ethyl acetate/ether (445 mg, 30%): m.p. 88.5-90.5°C.
Analysis Calc. for: $C_{21}H_{23}N_2O_4 \cdot 1/2H_2O$: C 67.01, H 6.43, N 7.44; found: C 67.20, H 6.59, N 7.53.

EXAMPLE 14

1-(4-Nitrobenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-)3,4-dimethoxyphenyl)butyrate (1.01 g, 4.0 mmol) and 4-nitrobenzaldehyde (0.60 g, 4.0 mmol) in chloroform under an argon atmosphere was heated at reflux for 2.5 hours. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 4 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and a solution of sodium cyanoborohydride (0.50 g, 8.0 mmol) in methanol was added. The mixture was stirred at 0°C for 1 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between 10% ethyl acetate/ether and dilute, cold sodium hydroxide. The aqueous layer was extracted, the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 40-80% ethyl acetate/methylene chloride, providing a solid of the title compound (560 mg, 39%): m.p. 100-101°C.
Analysis Calc. for: $C_{19}H_{20}N_2O_5 \cdot N \cdot 7.86$.

EXAMPLE 15

1-(4-Aminobenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-nitrobenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinone (500 mg, 1.40 mmol) in methanol (20 mL) and anhydrous tetrahydrofuran (10 mL) was treated with ammonium formate (1.06 g, 16.8 mmol) and 10% palladium on carbon (140 mg). The suspension was stirred for two hours under argon. The reaction was

then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water. After extracting, the organic layer was dried (sodium sulfate) and concentrated *in vacuo* to provide the title compound (303 mg, 64%).

Analysis Calc. for $C_{19}H_{22}N_2O_3 \cdot 5/8H_2O$: C 67.59, H 6.94, N 8.29; found: C 67.48, H 6.90, N 8.19.

EXAMPLE 16

1-(4-Dimethylaminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (0.5 g, 1.5 mmol) and 4-dimethylaminobenzaldehyde (0.27 g, 1.8 mmol) in chloroform under an argon atmosphere was heated at reflux for 2.5 hours. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran chilled in an ice bath and a solution of anhydrous hydrochloric acid in ether (1.0 M, 3.8 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and sodium cyanoborohydride (0.43 g, 6.9 mmol) was added. The mixture was stirred 0°C for 3 h, at 5°C for 16 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between 10% ethyl acetate/ether and dilute, cold sodium hydroxide. The aqueous layer was extracted, the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed *in vacuo*, the residue was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed overnight. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 67-75% ethyl

acetate/hexanes, provided a resin of the title compound (366 mg, 60%).
Analysis Calc. for $C_{25}H_{32}N_2O_3 \cdot 1/4H_2O$: C 72.70, H 7.93, N 6.78; found: C 72.76, H 7.80, N 6.74

EXAMPLE 17

1-(4-N-Carbomethyoxycarbamamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.2 g, 0.53 mmol) in dry methylene chloride and N-methylmorpholine (70 mL, 0.64 mmol) at zero degrees, was treated dropwise with methyl oxalylchloride (54 mL, 0.58 mmol). After stirring overnight, and addition additional methyl oxalyl chloride (108 mL), the reaction mixture was partitioned between ice cold aqueous sodium bicarbonate and methylene chloride, the organic phase washed with water and concentrated *in vacuo* to a crude solid of the title compound which was recrystallized from ethyl acetate/ether (210 mg, 85%); m.p. 134-136°C.
Analysis Calc. for $C_{26}H_{30}N_2O_6 \cdot 1/8H_2O$: C 66.62, H 6.50, N 5.98; found: C 66.54, H 6.57, N 5.95.

EXAMPLE 18

1-(4-Carboxycarbamidobenzyl)-4-(30cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-N-carbomethyoxy-carbamaidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (95 mg, 02 mmol) prepared as described in Example 17 in methanol was treated with pulverized lithium hydroxide monohydrate (26 mg, 0.6 mmol) and stirred under an argon atmosphere for 1.5 hours. The solvent was removed *in vacuo* and the residue was added to a mixture of ice and 3N hydrochloric acid to

precipitate a white solid of the title compound (73 mg, 81%): m.p. 167.5-170°C (decomposed).
Analysis Calc. for $C_{25}H_{28}N_2O_6 \cdot 5/8H_2O$: C 64.75, H 6.36, N 6.04; found: C 64.83, H 6.43, N 6.02.

EXAMPLE 19

1-(4-Methanesulfonamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (200 mg, 0.53 mmol) in anhydrous pyridine (3 mL) under argon was treated with methanesulfonylchloride (60 mL 0.79 mmol) dropwise, The solution was heated at 60°C for 30 min and then at reflux for two hours. The reaction was partitioned between ice cold aqueous acid and ethyl acetate and the organic layer was dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography eluting with 75-90% ethyl acetate/hexanes, to provide a cream colored foam of the title compound (107 mg, 44%).
Analysis Calc. for $C_{24}H_{30}N_2O_2S \cdot 1/3H_2O$: C 62.05, H 6.65, N 6.03; fund: C 62.11, H 6.62, N 6.04.

EXAMPLE 20

1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

1-(4-Carbomethoxybenzyl)-4-(3cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-)3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.57 g, 4.9 mmol) and 4-carbomethoxybenzaldehyde (0.82 g, 5.0 mmol) in chloroform under an argon atmosphere was stirred overnight at room temperature and heated at reflux for 2 h the next day. The mixture was cooled, the solvent was removed *in vacuo* and the residue was redissolved in tetrahydrofuran and a solution of

anhydrous hydrochloric acid in ether (1.0 M, 6.5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol chilled in an ice bath and sodium cyanoborohydride (0.47 g, 7.4 mmol) was added. The mixture was stirred at 0°C for 2 h, kept at 5° for 16 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between methylene chloride and dilute, cold sodium hydroxide. The aqueous layer was extracted with methylene chloride and the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed overnight. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 40-75% ethyl acetate/hexanes, provided a solid of the title compound (1.1 g, 53%): m.p. 98-99°C. Analysis Calc. for $C_{25}H_{29}NO_5$: C 70.90, H 6.90, N 3.31; found: C 70.69, H 6.89, N 3.35.

EXAMPLE 21

1-(4-Methylsulfonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-methylthiobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.5 g, 123 mmol) in methylene chloride was cooled to 0°C and treated with m-chloroperoxybenzoic acid (80%, 0.43 g, 2.4 mmol). The reaction was allowed to stir under an argon atmosphere for 3.5 hours. The reaction was diluted with methylene chloride and washed three times with saturated aqueous sodium bicarbonate, once with water and once with brine. The organic layer was dried (potassium carbonate) and the solvent was removed *in*

vacuo to provide the title compound (0.5 g, 92%), which foamed under vacuum.
Analysis Calc. for $C_{24}H_{29}NO_5S \cdot 1/2H_2O$: C 63.69, H 6.68, N 3.09, S 7.08; found: C 63.69, H 6.42, N 3.12, S 6.91.

EXAMPLE 22

1-(3,4-Dimethyoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.5 g, 4.9 mmol) and 3,4-dimethyoxybenzaldehyde (0.85 g, 5.1 mmol) in chloroform under an argon atmosphere was heated at reflux for two hours and then allowed to stir overnight at room temperature. The solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and sodium cyanoborohydride (0.5 g, 8.0 mmol) was added. The mixture was stirred at room temperature for 4.5 h, partitioned between 1:1 ethyl acetate/ether and 5% sodium hydroxide and the organic layer dried (sodium sulfate). The solvent was removed *in vacuo* and toluene and a catalytic amount of sodium cyanide were added to the oil. The reaction stirred overnight at room temperature and was heated to reflux for six hours. The toluene was removed under reduced pressure and the residual oil was partitioned between methylene chloride and water. The organic layer was dried (sodium sulfate). The residue was purified by flash chromatography, eluting with 95:5 chloroform/methanol to provide an oil of the title compound (1.6 g, 75%).
Analysis Calc. for $C_{24}H_{31}NO_5 \cdot 1/4SiO_2$: C 68.16, H 7.09, N 3.18; found: C 68.12, H 6.96, N 3.05.

EXAMPLE 23

1-(4-Methylthiobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.5 g, 4.9 mmol) and 4-methylthiobenzaldehyde (0.78 g, 5.1 mmol) in chloroform under an argon atmosphere was heated at reflux for two hours and then allowed to stir overnight at room temperature. The solvent was removed *in vacuo* and the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and sodium cyanoborohydride (0.5 g, 8.0 mmol) was added. The mixture was stirred at room temperature for 4.5 h, partitioned between 1:1 ethyl acetate/ether and 5% sodium hydroxide and the organic layer dried (sodium sulfate). The solvent was removed *in vacuo* and toluene and a catalytic amount of sodium cyanide were added to the oil. The reaction stirred overnight at reflux temperature and then was stirred at room temperature for six hours. The toluene was removed under reduced pressure and the residual oil was partitioned between methylene chloride and aqueous acid. The organic layer was dried (sodium sulfate). The residue was purified by flash chromatography, eluting with 98:3 chloroform/methanol to provide an oil of the title compound (1.7 g, 85%).

Analysis Calc. for $C_{24}H_{29}NO_3S \cdot 1/4SiO_2$: C 67.57, H 6.85, N 3.28; found: C 67.42, H 6.82, N 3.19.

EXAMPLE 24

1-(4-Methylsulfoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

To an ice cold solution of sodium periodate (201 mg, 0.94 mmol) and water under an argon atmosphere was added a solution of 1-(4-methylthiobenzyl)-4-(3-cyclopentyloxy--4-methoxyphenyl)-2-pyrrolidinone (352 mg, 0.86 mmol) in methanol (8 mL). The reaction mixture was allowed to warm to room temperature and then stirred overnight. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water and extracted three times. The organic layer was dried (potassium carbonate) and the solvent removed to provide an oil of the title compound (370 mg, 71%). Analysis Calc. for $C_{24}H_{29}NO_4S \cdot 1/4SiO_2$: C 65.13, H 6.60, N 3.16; found: C 65.26, H 6.66, N 3.14.

EXAMPLE 25

1-(2-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) 1-(2-Nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (0.5 g, 1.65 mmol) and 2-nitrobenzaldehyde (0.26 g, 1.72 mmol) in chloroform under an argon atmosphere wad heated at reflux for 9 h. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 1.72 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled with an ice bath and a solution of sodium cyanoborohydride (0.21 g, 3.3 mmol) in methanol was added. The mixture was kept at 5°C for 18 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between ether containing ethyl

acetate and a solution of cold, dilute sodium hydroxide and the organic layer dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and refluxed for 15 hours. The solvent was removed *in vacuo*, the residue was partitioned between ethyl acetate and water and the organic layer washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 1:1% ethyl acetate/hexanes, to provide the product (468 mg, 69%).

b) 1-(2-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(2-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.47 g, 1.14 mmol) in methanol (20 mL) and anhydrous tetrahydrofuran (5 mL) was treated with ammonium formate (0.95 g, 15.1 mmol) and 10% palladium on carbon (110 mg). The suspension was stirred for 18 h under argon. The reaction was then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and ice water. After extracting, the organic layer was washed with water, dried (sodium sulfate) and concentrated *in vacuo* to provide a colorless oil (434 mg, 100%).

c) 1-(2-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(2-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.43 g, 1.14 mmol) in dry pyridine cooled to 0°C was treated dropwise with acetic anhydride (216 mL, 2.28 mmol). After stirring overnight, the reaction mixture was partitioned between ice cold aqueous hydrochloric acid and ethyl acetate, the aqueous phase extracted, and the combined organic layers washed with

aqueous hydrochloric acid, water, aqueous sodium bicarbonate and dried (sodium sulfate). The solution was concentrated *in vacuo* to provide a foam of the title compound (293 mg, 60%).

Analysis Calc. for $C_{25}H_{30}N_2O_4$: C 70.07, H 7.21, N 6.54; found: C 70.07, H 7.02, N 6.40.

EXAMPLE 26

1-(3-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A) 1-(3-Nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (0.5 g, 1.65 mmol) and 3-nitrobenzaldehyde (270 mg, 1.79 mmol) in chloroform under an argon atmosphere was heated at reflux for 9 h. The mixture was cooled, the solvent was removed *in vacuo* and the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 1.65 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and a solution of sodium cyanoborohydride (0.24 g, 3.8 mmol) in methanol was added. This mixture was kept at 5°C for 18 h, warmed to 20°C, concentrated *in vacuo* and the residue partitioned between ether containing ethyl acetate and a solution of cold, dilute sodium hydroxide and the organic layer dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and refluxed for 40 hours. The solvent was removed *in vacuo*, the residue was partitioned between ethyl acetate and water and the organic layer washed with two times. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 40-66% ethyl acetate/hexanes to provide a yellow oil (0.44 g, 64%).

b) 1-(3-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(3-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.44 g, 1.06 mmol) in methanol (20 mL) and anhydrous tetrahydrofuran (5 mL) was treated with ammonium formate (1.0 g) and 10% palladium on carbon (110 mg). The suspension was stirred for 2 h under argon. The reaction was then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water. After extracting, the organic layer was dried (sodium sulfate) and concentrated *in vacuo* to provide a colorless oil of the title compound (403 mg, 100%).

c) 1-(3-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(3-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.40 g, 1.06 mmol) in dry pyridine at 0°C, was treated dropwise with acetic anhydride (200 mL, 2.12 mmol). After stirring overnight, the reaction mixture was partitioned between ice cold aqueous hydrochloric acid and ethyl acetate, the aqueous layer extracted, and the combined organic layers washed with aqueous hydrochloric acid, water, aqueous sodium bicarbonate and dried (sodium sulfate). The solution was concentrated *in vacuo* to provide a solid of the title compound (332 mg, 69%): m.p. 145-146.5°C. Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/8H_2O$: C 70.69, H 7.18, N 6.59; found: C 70.72, H 7.27, N 6.49.

EXAMPLE 27

1-(4-Trifluoromethylsulfonamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl-2-pyrrolidinone

A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (224 mg, 0.57 mmol) and triethylamine (160 mL, 1.15 mmol) in anhydrous methylene chloride (4 mL) cooled to -78°C was treated with triflic anhydride (106 mL, 0.63 mmol) dropwise. After five minutes, some starting material was left, so additional triflic anhydride (35 mL, 0.21 mmol) was added. The solvent was removed *in vacuo* and the resin was partitioned between aqueous sodium bicarbonate and ethyl acetate and extracted. The organic layer was washed with dilute cold aqueous acid, water and dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 75:25 ethyl acetate/hexanes to provide a foam of the title compound (133 mg, 46%). Analysis Calc. for $C_{24}H_{27}N_2O_5F_3S$: C 56.24, H 5.31, N 5.47; fund: C 56.54, H 5.62, N 5.47.

EXAMPLE 28

1-(4-Carboxyamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphyenyl)-2-pyrrolidinone

A solution of 1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as in Example 20 (300 mg, 0.71 mmol) in methanol with sodium cyanide (13 mg, 0.27 mmol) in a sealed glass bomb was cooled to zero degrees and saturated with ammonia. The reaction was slowly heated at 50-55°C for a total of six days. The solvent was removed *in vacuo* to yield the crude product, which was purified by flash chromatography, eluting with 4-6% methanol/methylene chloride, to provide a white solid of the title compound (174 mg, 60%): m.p. 164-165°C.

Analysis Calc. for $C_{24}H_{28}N_2O_4$: C 70.57, H 6.91, N 6.86; found: C 70.47, H 6.81, N 6.90.

EXAMPLE 29

1-(2,4-Diaminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) 1-(2,4-Dinitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphyenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.52 g, 4.95 mmol) and 2,4-dinitrobenzaldehyde (0.98 g, 5.0 mmol) in chloroform under an argon atmosphere was heated at reflux for 2 h. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 6.5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and to this solution chilled in an ice bath sodium cyanoborohydride (0.44 g, 7.0 mmol) was added. The mixture was stirred at room temperature for 15 h, concentrated *in vacuo* and the residue partitioned between ether containing ethyl acetate and a solution of cold, dilute sodium hydroxide and the organic layer dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and refluxed for 15 hours. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 40-60% ethyl acetate/hexanes and recrystallized from ethyl acetate, to provide a tan solid (1.09 g, 48%): m.p. 125.5-127°C.

b) 1-(2,4-Diaminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(2,4-dinitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-

pyrrolidinone (0.1 g, 0.22 mmol) in methanol (7 mL) and anhydrous tetrahydrofuran (2.5 mL) was treated with ammonium formate (0.4 g) and 10% palladium on carbon (40 mg). The suspension was stirred for 2 h under argon. The reaction was then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between chloroform and water. After extracting, the organic layer was dried (potassium carbonate) and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 0-2% methanol/ethyl acetate, to provide a resin of the title compound (70 mg, 79%).

Analysis Calc. for $C_{23}H_{29}N_3O_3 \cdot O \cdot 29H_2O$: C 68.97, H 7.44, N 10.49; found: C 69.26, H 7.36, N 10.09.

EXAMPLE 30

1-(4-oxamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-carboxycarbamido-benzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (458 mg, 0.99 mmol) in dimethoxyethylene glycol and N-methylmorpholine (200 mL, 1.82 mmol) was treated with isobutyl chloroformate (230 mL, 1.8 mmol). Liquid ammonia (5 mL) was condensed in a separate flask, and to it dimethoxyethylene glycol (10 mL) was added. Approximately ten minutes after the isobutyl chloroformate was added to the flask, part of the ammonia/ethylene glycol dimethyl ether solution (ca. 2-5 mL) was added to the reaction flask. After 45 min, the solvent was removed *in vacuo* and the residue was dissolved in chloroform and washed twice with cold aqueous acid and twice with water. The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to yield a resin, which was purified by flash chromatography, eluting with a gradient of 70-100% ethyl acetate/methylene chloride and finally with 99:1 ethyl

acetate/methanol. The title compound (190 mg, 43%) was a white solid: m.p. 180-182°C.
Analysis Calc. for $C_{25}H_{29}N_3O_5$: C 66.50, H 6.47, N 9.31; found: C 66.66, H 6.47, N 9.57.

EXAMPLE 31

1-(2,4-Diacetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(2,4-diaminobenzyl)040(30-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as described in Example 29 (0.22 g, 0.55 mmol) in dry pyridine at 0°C was treated dropwise with acetic anhydride (209 mL, 2.20 mmol). After stirring overnight, the reaction mixture was partitioned between ice cold aqueous hydrochloric acid and ethyl acetate, the aqueous layer extracted, and the combined organic layers washed with aqueous hydrochloric acid, water, aqueous sodium bicarbonate and dried (sodium sulfate). The solution was concentrated *in vacuo*, giving a resin which was purified by flash chromatography, eluting with 1:99 methanol/ethyl acetate to provide, a resin of the title compound (167 mg, 63%).
Analysis Calc. for $C_{27}H_{33}N_3O_5 \cdot 1/4H_2O$: C 66.99, H 6.98, N 8.68; fund: C 66.73, H 6.93, N 8.52.

EXAMPLE 32

1-(4-Cyanobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (2.1 g, 6.8 mmol) and 4- cyanobenzaldehyde (1.1 g, 8.2 mmol) in chloroform under an argon atmosphere was stirred for 72 h at room temperature and then heated at reflux for 1.25 h. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran

and a solution of anhydrous hydrochloric acid in ether (1.0 M, 9.0 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and to this solution chilled to 0°C sodium cyanoborohydride (0.6 g, 9.5 mmol) was added. The mixture was stirred at room temperature overnight, partitioned between methylene chloride and dilute, cold sodium hydroxide. The aqueous layer was extracted, and the combined organic layers washed with water and dried (potassium carbonate). The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 75% ethyl acetate/hexanes, provided a slid of the title compound (1.4 g, 44%): m.p. 92-93°C.

Analysis Calc. for $C_{24}H_{26}N_2O_3$: C 73.82, H. 6.71, N 7.17; found: C 73.78, H 6.95, N 7.12

EXAMPLE 33

1-[4-(1-Imidazo)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (0.46 g, 1.4 mmol) and 4-(1-imidazo)benzaldehyde (0.29 g, 1.7 mmol) in chloroform under an argon atmosphere was heated at reflux for one hour. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 2.0 mmol) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and a solution of sodium cyanoborohydride (0.15 g, 2.3 mmol) in methanol was added. The mixture warmed to 20°C over 1.5 h, was kept at 5°C for 16 h and concentrated *in vacuo*. The residue was partitioned

between methylene chloride and dilute, cld sodium hydroxide. The organic layer was washed with water and dried (potassium carbonate). The residue after concentration, was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed for 24 h. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water tow times. The organic layer was dried (sodium sulfate) and evaporated. Purification by successive flash chromatographies, first with a gradient of 2-10% methanol/chloroform and then with a gradient of -=2% methanol in chloroform (equilibrated with ammonium hydroxide and dried over potassium carbonate) provided a brittle resin of the title compound (159 mg, 26%).

Analysis Calc. for $C_{26}H_{29}N_3O_3 \cdot 1/2H_2O$: C 70.89, H 6.86, N 9.53; found: C 70.91, H 7.12, N 9.29.

EXAMPLE 34

1-(4-hydroxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (2.1 g, 6.6 mmol) and 4-hydroxybenzaldehyde (0.94 g, 7.5 mmol) in chloroform under an argon atmosphere was heated at reflux for 1.5 h. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 7.4 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and sodium cyanoborohydride (0.55 g, 8.7 mmol) was added. The mixture was warmed to room temperature overnight, concentrated *in vacuo* and the residue partitioned between methylene chloride and dilute, cld sodium hydroxide. The organic layer was washed with water and dried (sodium sulfate). The residue was dissolved in

toluene with a catalytic amount of sodium cyanide and was refluxed for 1.5 h. The solvent was removed *in vacuo*, the residue was dissolved in methylene chloride and washed with water two times. The organic layer was dried (potassium carbonate) and evaporated. Purification by flash chromatography, eluting with 50-90% ethyl acetate/hexanes, and crystallization from ethyl ether.provided a solid of the title compound (934 mg, 37%): m.p. 118-120°C.

Analysis Calc. for $C_{23}H_{27}NO_4$: C 72.42, H 7.13, N 3.67; found: C 72.33, H 7.17, N 3.59.

EXAMPLE 35

1-[Ethyl 2-(4-aminophenyl)acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) Methyl 4-[N-(4-t-Butoxycarbonylamino-1-carboethoxybenzyl)amine]-3(3-cyclopentyloxy-4-methoxyphenyl)-butanoate To a solution of methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate (484 mg, 1.6 mmol) in methanol (20 mL) was added 70% perchloric acid (155 mL, 1.7 mmol) and 10% palladium on carbon (12 mg). The resulting mixture was hydrogenated at 50 psi for 2 h and filtered through a pad of celite. The filtrate was concentrated *in vacuo*. The solid residue was partitioned between methylene chloride and aqueous sodium carbonate, washed an additional time with aqueous sodium bicarbonate and the organic layer was dried (sodium sulfate). The solvent was removed *in vacuo*, the residue dissolved in dimethylformamide (5 mL) and treated with ethyl 2-chloro-2-(4-t-butoxycarbonylaminophenyl)acetate (503 mg, 1.6 mmol), sodium iodide (240 mg, 0.32 mmol) and triethylamine (225 mL, 1.6 mmol). After stirring at room temperature under an argon atmosphere for 1 h, the residue was partitioned between ether and water and extracted several times. The organic extract was dried (magnesium sulfate) and

evaporated. Purification by flash chromatography, eluting with 3:7 ethyl acetate/hexanes, provided the product (718 mg, 77%).

b) 1-[Ethyl 2-(4-t-butoxycarbonylaminophenyl)acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of Methyl 4-[N-(4-t-butoxycarbonylamino-1-carboethoxybenzyl)amine]-3-(3-cyclopentyloxy-4-methoxyphenyl)butanoate (1.8 g, 309 mmol) in dimethylformamide (30 mL) was treated with a catalytic amount of sodium cyanide and dimethylaminopyridine (378 mg, 3.1 mmol) and heated at 95-100°C for 20 h. The reaction mixture was partitioned between ether and water several times and the organic extracts were dried (magnesium sulfate) and evaporated. Purification by flash chromatography, eluting with 4:6 ethyl acetate/hexanes,provided a yellow foam (840 mg, 49%).

c) 1-[Ethyl 2-(4-aminophenyl)acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-[ethyl 2-(4-t-butoxycarbonylamino-phenyl)acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (920 mg, 1.67 mmol) in methylene chloride (20 mL) was cooled to 0°C and treated with trifluoroacetic acid(20 mL) and stirred at room temperature for 24 h. The reaction was quenched by adding solid sodium bicarbonate and the reaction mixture was partitioned between methylene chloride and water. The organic extract was dried (potassium carbonate) and evaporated. Purification by flash chromatography, eluting with 4:6 ethyl acetate/hexanes, provided the product (647 mg, 86%).
Analysis Calc. for $C_{26}H_{32}N_2O_5 \cdot 1H_2O$: C 66.36, H 7.28, N 5.95; found: C 66.11, H 6.89, N 5.66.

EXAMPLE 36

1-[Ethyl 2-(4-acetamidophenyl)acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-[ethyl 2-(4-aminophenyl)acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (53.4 mg, 0.12 mmol) in methylene chloride (0.25 mL) was treated dropwise with a solution of acetic anhydride (35 mL, 0.36 mmol) in methylene chloride (1 mL) and pyridine (3 drops). After stirring for 3 h under an argon atmosphere, the reaction mixture was purified by flash chromatography, eluting with 7:3 ethyl acetate/hexanes, to provide an oil of the title compound (55.1 mg, 94%).

Analysis Calc. for $C_{28}H_{34}N_2O_6$: C 68.00, H 6.93, N 5.66; found: C 67.91, H 7.18, N 5.54.

EXAMPLE 37

1-[2-(4-Acetamidophenyl)acetic acid]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-[ethyl 2-(4-aminophenyl)-acetato]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (212 mg, 0.43 mmol) in ethanol (5 mL) was treated with lithium hydroxide monohydrate (55 mg, 1.29 mmol) and stirred for 1 h. The solvent was removed *in vacuo* and the resin was dissolved in water and acidified with 10% aqueous hydrochloric acid. The product was extracted with 95:5 methylene chloride/methanol and the organic extract was dried (magnesium sulfate) and evaporated to provide the title compound (174 mg, 88%).

Analysis Calc. for $C_{26}H_{30}N_2O_6 \cdot 3/8H_2O$: C 65.98, H 6.55, N 5.92; found: C 65.94, H 6.54, N 5.79.

EXAMPLE 38

1-(4-Aminothiocarbonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-cyanobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, prepared as in Example 32 (850 mg, 2.18 mmol) in methanol (25 mL) in a pressure vessel, was treated with ammonium sulfide (15 mL, 53 mmol of a 23.9% solution). The vessel was sealed and the reaction stirred for 1 h at 65-75°C. The reaction mixture was concentrated *in vacuo*, water added and the aqueous phase extracted three times with methylene chloride. The extracts were washed with water two times, dried (sodium sulfate) and evaporated to a yellow residue. The residue was crystallized from ethanol/water. Purification by flash chromatography, eluting with 60-75% ethyl acetate/methylene chloride followed by crystallization from ethyl acetate/ethyl ether provided a yellow solid (682 mg, 74%): m.p. 85.5-87.5°C.
Analysis Calc. for $C_{24}H_{28}N_2O_3S$: C 67.90, H 6.65, N 6.60; found: C 67.63, H 6.81, N 6.38.

EXAMPLE 39

1-(4-Methylmercaptocarbiminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydroiodide

A solution of 1-(4-aminothiocarbonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from Example 38 (290 mg, 0.68 mmol)in acetone (4 mL) was treated with methyl iodide (100 mL, 1.61 mmol). The reaction was capped and stirred for 18 h at room temperature. Ethyl ether was added to complete the formation of a cream colored solid which was removed by filtration and washed with ether (336 mg, 87%): m.p. 170-172°C.

Analysis Calc. for $C_{25}H_{30}N_2O_3S \cdot HI$: C 53.01, H 5.52, N 4.95; found: C 52.99, H 5.51, N 4.68.

EXAMPLE 40

1-(4-Formamidiniumbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone acetate

A suspension of 1-(4-methylmercapto-carbiminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydroiodide prepared as in Example 39 (350 mg, 0.62 mmol) and ammonium acetate (151 mg, 1.95 mmol) in ethanol (1.8 mL) was heated at 90-95°C under an argon atmosphere for 1 h. The reaction mixture was allowed to cool, and the white crystals were collected and washed sequentially with methanol and ethyl ether (234 mg, 78%): m.p. 186-188°C.
Analysis Calc. for $C_{24}H_{29}N_3O_3 \cdot C_2H_4O \cdot H_2O$: C 64.31, H 7.26, N 8.65; found: C 64.63, H 7.32, N 8.56.

EXAMPLE 41

1-[4-(2-Imidazo)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of the 1-(4-formamidiniumbenzyl)-4-(3-cyclopentyloxy-4-methoxy-phenyl)-2-pyrrolidinone acetate of Example 40 (183 mg, 0.38 mmol) in chloroform was treated with 10% sodium hydroxide and ice. This mixture was extracted with chloroform, and the organic layer dried (potassium carbonate) and evaporated to a residue of the formamidine. The residue was dissolved in chloroform (20 mL) under an argon atmosphere and was treated with chloroacetaldehyde (113 mL, 0.28 mmol of a 50% aqueous solution) and triethylamine (119 mL, 0.86 mmol). The mixture was heated at reflux for 5 h and allowed to stir at room temperature for 86 h. The solvent was removed *in vacuo* and the residue was purified by flash chromatography and eluted with 0.5-1% methanol/chloroform. The residue was dissolved in ethyl

acetate/ethanol and extracted with cold 10% aqueous hydrochloric acid. The acid extracts were washed four times with ethyl acetate and the aqueous layer made alkaline with aqueous sodium carbonate and extracted three times with methylene chloride. The combined methylene chloride phase was dried (potassium carbonate) and evaporated to provide a brittle resin (44 mg, 27%). Analysis Calc. for $C_{26}H_{29}N_3O_3 \cdot 1/2H_2O$: C 70.89, H 6.86, N 9.54; found: C 70.95, H 6.75, N 9.21.

EXAMPLE 42

1-(4-Dimethylaminocarbonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-carboxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from Example 3 (225 mg, 0.62 mmol) in tetrahydrofuran (15 mL) under an argon atmosphere was treated with the dropwise addition of N-methylmorpholine (112 mL, 1.02 mmol). In a second flask, dimethylamine (15 mL) was bubbled into a -78°C solution of dry tetrahydrofuran (15 mL). The solution of the acid and the N-methylmorpholine was then treated with isobutyl chloroformate (135 mL, 10.2 mmol) and allowed to stir for 7 min under an argon atmosphere. The mixed anhydride suspension was transferred via cannula to the flask containing the amine and the cold bath was removed. After 15 min, the reaction was concentrated *in vacuo* and partitioned between ethyl acetate and aqueous sodium carbonate. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with water, dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 4-6% methanol in ethyl acetate, provided a resin (104 mg, 38%).
Analysis Calc. for $C_{26}H_{32}N_2O_4 \cdot 1/5H_2O$: C 70.95, H 7.42, N 6.36; found: C 70.94, H 7.26, N 6.31.

EXAMPLE 43

1-(4-Acetoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-hydroxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, prepared as in Example 34 (239 mg, 0.63 mmol) in pyridine (2 mL) at 0°C was treated with the dropwise addition of acetic anhydride (160 mL, 1.7 mmol) and allowed to stir for 72 h under an argon atmosphere. The reaction was poured into ice cold aqueous hydrochloric acid and extracted twice with ethyl acetate. The organic extracts were washed with cold dilute hydrochloric acid, cold water and cold aqueous sodium bicarbonate. The extracts were dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 60% ethyl acetate/hexanes, provided a resin (148 mg, 55.5%).

Analysis Calc. for $C_{25}H_{29}NO_5$: C 70.90, H 6.90, N 3.31; found: C 70.71, H 7.00, N 3.25.

EXAMPLE 44

1-(4-Acetamido-2-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) 1-4-Amino-2-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, and 1-(2-Amino-4-nitrobenzyl)040(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A suspension of 1-(2,4-dinitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from Example 29 (426 mg, 0.94 mmol) in ethanol (60 mL) was treated with three portions of ammonium sulfide (1.67 g total, 23.9% solution in ethanol, 5.9 mm total) and heated to reflux for 10 min after each addition and subsequently allowed to stir at room temperature for 18 h under an argon atmosphere. The solvent was removed *in vacuo* and the residue purified by flash chromatography.

Elution with 50-60% ethyl acetate/hexanes afforded the 2-amino-4-nitro isomer (140 mg, 35%) while continued elution with 70-90% ethyl acetate/hexanes provided the 4-amino-2-nitro isomer (180 mg, 45%).

b) 1-(4-Acetamido-2-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A solution of 1-(4-amino-2-nitrobenzylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (180 mg, 0.42 mmol) in pyridine cooled to 0°C was treated dropwise with acetic anhydride (105 mL, 1.1 mmol). The reaction was allowed to stir for 18 h at room temperature under an argon atmosphere. The reaction was poured into ice cold aqueous hydrochloric acid and extracted twice with ethyl acetate. The organic extracts were washed with cold dilute hydrochloric acid, cold water and cold aqueous sodium bicarbonate. The extracts were dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 60% ethyl acetate/hexanes, provided a resin (200 mg, 100%).

c) 1-(4-Acetamido-2-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A solution of 1-(2-nitro-4-acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (814 mg, 0.42 mmol) in methanol (4 mL) and tetrahydrofuran (3 mL) was treated with 10% palladium on carbon (43 mg) and ammonium formate (400 mg, 6.35 mmol). The reaction was allowed to stir under argon for 5 h, then filtered through celite. The solvent was removed *in vacuo* and the residue was partitioned between cold aqueous sodium carbonate and chloroform. The organic extracts were washed with water, dried (potassium carbonate) and evaporated. Purification by flash chromatography, eluting with 75-100% ethyl acetate/methylene chloride, followed by recrystallization from warm ethyl acetate

and washing with ether provided orange crystals (35 mg, 20%): m.p. 184-186°C.
Analysis Calc. for C25H31N3O4.1/4H2O: C 67.93, H 7.18, N 9.51; found: C 68.08, H 7.13, N 9.22.

EXAMPLE 45

1-(2-Acetamido-4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(2-amino-4-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphyenyl)-2-pyrrolidinone from Example 44 (140 mg, 0.33 mmol) in pyridine cooled to 0°C was treated dropwise with acetic anhydride (100 µL, 1.1 mmol). The reaction mixture was allowed to stir for 24 h at room temperature under an argon atmosphere, and submitted to another two cycles of treatment with acetic anhydride (200 mL, 2.2 mmol; 400 µL, 4.4 mmol). The reaction was poured into ice cold aqueous hydrochloric acid and extracted twice with methylene chloride. The organic extracts were washed with cold dilute hydrochloric acid, cold water and 10% aqueous sodium hydroxide. The extracts were dried (potassium carbonate) and evaporated to provide an oil (114 mg, 74%). 1-(2-Acetamido-4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A solution of 1-(4-nitro-2-acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (114 mg, 0.24 mmol) in methanol (10 mL) and tetrahydrofuran (1.5 mL) was treated with 10% palladium on carbon (32 mg) and ammonium formate (246 mg, 3.9 mmol). The reaction was allowed to stir under argon for 4 h, then filtered through celite. The solvent was removed *in vacuo* and the residue was partitioned between cold aqueous sodium carbonate and methylene chloride. The organic extracts were washed with water, dried (potassium carbonate) and evaporated to provide a glass (75 mg, 71%).

Analysis Calc. for $C_{25}H_{31}N_3O_4$: C 68.63, H 7.14, N 9.60; fund: C 68.63, H 7.25, N 9.40.

EXAMPLE 46

1-[3-(2-Chloroacetamido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

To a mixture of 1-(3-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.23 g, 0.6 mmol) and powdered sodium carbonate (0.13 g, 1.21 mmol) in dry acetone (4 mL) under an argon atmosphere at room temperature was added dropwise chloroacetyl chloride (0.09 mL, 1.13 mmol). After stirring for 4h, the solvent was removed under a stream of argon and the residue was partitioned between methylene chloride and ice water containing dilute hydrochloric acid. The aqueous layer was extracted three times with methylene chloride, the combined organic extract was dried (sodium sulfate) and the solvent was removed *in vacuo*. Half of the residue was purified by flash chromatography, eluting with 1:1 ether/methylene chloride, and the other half was purified by flash chromatography, eluting with 45-60% ethyl acetate/methylene chloride, to provide a foam of the title compound (0.22 g, 80%).
Analysis Calc. for $C_{25}H_{29}ClN_2O_4$: C 65.71, H 6.40, N 6.13; found : C 65.72, H 6.40, N 5.99.

EXAMPLE 47

1-[4-(2-Chloroacetamido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

1-[4-(2-Chloroacetamido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone To a mixture of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-

pyrrolidinone (0.35 g, 0.92 mmol) and powdered sodium carbonate (0.195 g, 1.84 mmol) in dry acetone (8 mL) under an argon atmosphere at room temperature was added dropwise chloroacetylchloride (0.132 mL, 1.66 mmol). After stirring for 1.5h, the solvent was removed and the residue was partitioned between methylene chloride and ice water containing dilute hydrochloric acid. The organic extract was washed twice with water, dried (soidum sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 45-60% ethyl acetate/methylene chloride, and the product was triturated with ether to provided a white solid (0.35 g, 83%): of the title compound: m.p. 138-139°C.

Analysis Calc. for $C_{25}H_{29}ClN_2O_4$: C 65.71, H 6.40, N 6.13; found : C 65.74, H 6.36, N 6.06.

EXAMPLE 48

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(4,4-dimethyl-2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone

a) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(N-1-hydroxy-2-methyl-2-propylcarbamidocarbamido)benzyl]-2-pyrrolidinone To a solution of 1-(4-N-carbomethoxy-carbamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.125 g, 0.27 mmol) in alumina-treated chloroform (10 mL) was added 2-amino-2-methylpropanol (0.051 mL, 0.54 mmol) and the mixture was stirred under an argon atmosphere overnight. Additional 2-amino-2-methylpropanol (0.037 mL, 0.27 mmol) was added and stirring was continued for 8h. The chloroform was extracted with dilute hydrochloric acid, washed with water and dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash

chromatography, eluting with 2% methanol in chloroform, to provide an oil (0.106 g, 79%).

b) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(4,4-dimethyl-2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone To a solution of diethylaminosulfur trifluoride (0.054 mL, 0.4 mmol) in dry methylene chloride (15 mL) at -45°C under an argon atmosphere was added dropwise over 40 min a solution of 4-(3-cyclopentyl-oxy-4-methoxyphenyl)-1-[4-(N-1-hydroxy-2-methyl-2-propylcarbamidocarbamido)benzyl]-2-pyrrolidinone (0.106 g, 0.2 mmol) in dry methylene chloride (2.5 mL and then a 6 mL rinse). After 0.75h at -45°C, 5% aqueous sodium carbonate (5mL) was added, the mixture was allowed to warm to room temperature the organic layer was separated, dried (potassium carbonate) and evaporated. The residue was purified by flash chromatography, eluting with 2% methanol in chloroform, to provide a resin of the title compound (0.071 g, 70%).

Analysis Calc. for $C_{29}H_{35}N_3O_5$: C 68.89, H 6.98, N 8.31; found : C 68.56, H 6.94, N 8.18.

EXAMPLE 49

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone

a) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(N-2-hydroxyethylcarbamidocarbamidobenzyl]-2-pyrrolidinone To a solution of 1-(4-N-carbomethoxycarbamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.185 g, 0.4 mmol) in alumina-treated chloroform (10 mL) was added ethanolamine (0.049 mL, 0.81 mmol) and the mixture was stirred under an argon atmosphere overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 2-3% methanol in chloroform, and the product was triturated

with ether to provide a white solid (0.175 g, 89%): m.p. 133-134°C.

b) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone To a solution of diethylaminosulfur trifluoride (0.052 mL, 0.39 mmol) in dry methylene chloride (15 mL) at -40°C under an argon atmosphere was added dropwise over 40 min a solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-1-[4-(N-2-hydroxyethylcarbamidocarbamidobenzyl]-2-pyrrolidinone (0.13 g, 0.26 mmol) in dry methylene chloride (10 mL). After 1h at -40°C, additional diethylaminosulfur trifluoride (0.02 mL, 0.15 mmol) was added. After 1h, 5% aqueous sodium carbonate (4 mL) was added, the mixture was allowed to warm to room temperature the organic layer was separated, dried (potassium carbonate) and evaporated. The residue was purified by successive flash chromatographies, eluting in the first with 20% acetone in methylene chloride and in the second with 2.5% methanol in chloroform, to provide a white solid (0.05 g, 40%) of the title compound: m.p. 164-165°C.
Analysis Calc. for $C_{27}H_{31}N_3O_5$: C 67.91, H 6.54, N 8.80; found : C 67.75, H 6.53, N 8.62.

EXAMPLE 50

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-pyruvamidobenzyl)-2-pyrrolidinone

To 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.183 g, 0.48 mmol) in dry methylene chloride (7 mL) under an argon atmosphere at room temperature was added dropwise a solution of pyruvoyl chloride (39.1% in carbon tetrachloride, 0.1 mL, 0.48 mmol). After stirring for 4h, the mixture was poured into ice cold 5% aqueous sodium bicarbonate and

extracted three times with methylene chloride The organic extract was dried (sodium sulfate) and the solvent was removed *in vacuo*. The residue was combined with the product of a similar reaction conducted on 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (54 mg, 0.12 mmol) and was purified by flash chromatography, eluting with 20-25% ethyl acetate/methylene chloride. The product was triturated with ether to provided a solid of the title compound (0.20 g, 72%): m. p. 95-97°C.

Analysis Calc. for $C_{26}H_{30}N_2O_5$: C 69.31, H 6.71, N 6.22; found : C 69.02, H 6.59, N 6.29.

By the methods given above, the following compounds were made.

EXAMPLE 51

S-(-)-1-(4-Amino-3,5-dimethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A resin: Analysis Calc. for $C_{25}H_{32}N_2O_3 \cdot 1/2\ H_2O$: C 71.91, H 7.97, N 6.71; found : C 71.88, H 7.92, N 6.57.

EXAMPLE 52

S-(-)-1-(4-Acetamido-3,5-dimethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solid, m.p. 166-169°C: Analysis Calc. for $C_{27}H_{34}N_2O_4 \cdot 1/4\ H_2O$: C 71.26, H 7.64, N 6.16; found: C 71.27, H 7.54, N 6.04.

EXAMPLE 53

1-(4-Aminobenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone

A resin: Analysis Calc. for $C_{19}H_{18}F_4N_2O_3 \cdot 1/4\ H_2O$: C 56.65, H 4.63, N 6.95; found : C 56.71, H 4.62, N 6.80.

EXAMPLE 54

1-(4-Acetamidobenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone

A solid, m.p. 131-132°C: Analysis Calc. for $C_{21}H_{20}F_4N_2O_4$: C 57.27, H 4.58, N 6.36; found : C 57.15, H 4.64, N 6.21.

EXAMPLE 55

1-(4-Amino-3,5-dimethoxybenzyl)-4-(3,4-bis-difluoro-methoxyphenyl)-2-pyrrolidinone

A resin: Analysis Calc. for $C_{21}H_{22}F_4N_2O_3 \cdot 1/2\ H_2O$: C 57.93, H 5.32, N 6.48; found : C 58.15, H 5.16, N 6.31.

EXAMPLE 56

1-(4-Acetamido-3,5-dimethoxybenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone

A resin: Analysis Calc. for $C_{23}H_{24}F_4N_2O_4 \cdot 1/2\ H_2O$: C 57.85, H 5.28, N 5.87; found : C 58.03, H 5.23, N 5.69.

EXAMPLE 57

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-methoxymethyl-2-pyrrolidinone

An oil: Analysis Calc. for $C_{18}H_{25}NO_4$: C 67.69, H 7.89, N 4.39; found : C 67.50, H 7.77, N 4.34.

EXAMPLE 58

1-Benzyloxymethyl-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

An oil: Analysis Calc. for $C_{24}H_{29}NO_4 \cdot 1/4\ H_2O$: C 72.07, H 7.43, N 3.50; found : C 71.93, H 7.28, N 3.40.

EXAMPLE 59

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant formulation

A compound of formula I, (1 µg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Tablets/Ingredients	Per Tablet
1. Active ingredient (Cpd of Form. I)	40 mg
2. Corn Starch	20 mg
3. Alginic acid	20 mg
4. Sodium alginate	20 mg
5. Mg stearate	1.3 mg
	01.3 mg

Procedure for Tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

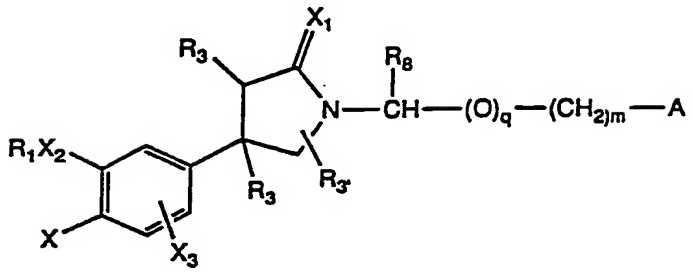
Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount f a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

CLAIMS:

1. A compound of the formula:



wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group; C_{4-6} cycloalkyl containing one or two unsaturated bonds; C_{7-11} polycycloalkyl, $(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_xOH$, $(CR_{14}R_{14})_sO(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_sO(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_y-R_{11}$, or $(CR_{14}R_{14})_z-R_{10}$;

X_1 is O or S;

X_2 is O or NR_{14};

X_3 is hydrogen or X;

X is YR_2, halogen, nitro, $NR_{14}R_{14}$, or formamide;

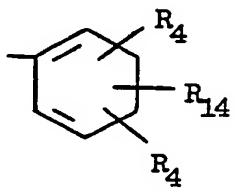
Y is O or S(O)m;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be unsubstituted or substituted by 1 to 5 fluorines;

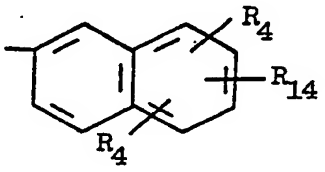
R_3 is hydrogen, halogen, CN, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, OR_5, $-CH_2OR_5$, $-NR_5R_{16}$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $C(O)NR_5R_{16}$, $-CH=CR_9R_9$, $-C\equiv CR_9$ or $-C(=Z)H$;

$R_{3'}$ is hydrogen, halogen, C_{1-4}alkyl, halo-substituted C_{1-4}alkyl, cyclopropyl unsubstituted or substituted by R_9, $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or $-C(=Z)H$;

A is



(a)



(b)

or

(c) C_{1-3} alkyl unsubstituted or substituted by one or more fluorines or one or two R_4 groups;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

x is an integer from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

R_4 is independently hydrogen, Br, F, Cl, $-NR_5R_6$, NR_6R_{16}, NO_2, $-C(Z)R_7$, $-S(O)_mR_{12}$, CN, OR_{16}, $-OC(O)NR_5R_{16}$, 1 or 2-imidazolyl, $-C(=NR_{16})NR_5R_{16}$, $-C(=NR_5)-SR_{12}$, $-OC(O)CH_3$, $-C(=NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$, $-NR_{16}-C(O)-R_{15}$, $-C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R_5 and R_{16} are as NR_5R_{16} they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4}alkyl, unsubstituted or substituted by one to three fluorines;

R_6 is H, R_{12}, $-C(O)R_{12}$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$, $-S(O)_mR_{12}$, $-S(O)_mCF_3$, $-C(=NCN)SR_{12}$, $-C(=NCN)R_{12}$, $-C(=NR_{16})R_{12}$, $-C(=NR_{16})SR_{12}$, or $-C(=NCN)NR_5R_{16}$,

R_7 is OR_5, $-NR_5R_{16}$, or R_{12};

R_8 is hydrogen, $C(O)R_7$, (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl-[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-,4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl);

R_9 is hydrogen, F or R_{12}.

R_{10} is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3}alkyl, halo substituted aryloxyC_{1-3}alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, furan, pyran, thiophene, thiopyran, C_{3-6} cycloalkyl, or a C_{4-6}cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{11} is 2-tetrahydropyran or 2-tetrahydro-thiopyran, 2-tetrahydrofuran or 2-tetrahydrothiophene unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group;

R_{12} is C_{1-4}alkyl unsubstituted or substituted by one to three fluorines;

R_{14} is independently hydrogen or a C_{1-2}alkyl unsubstituted or substituted by fluorine;

R_{15} is C_{1-4} alkyl unsubstituted or substituted by one or more halogens; $-C(O)C_{1-4}$ alkyl, unsubstituted or substituted by one or more halogens; oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, or pyrrolyl, and each of the heterocyclics may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{16} is OR_5 or R_5;

Z is O, $-NR_{12}$, $-NOR_5$, NCN, $-C(-CN)_2$, $-CR_5NO_2$, $-CR_5C(O)OR_{12}$, $-CR_5C(O)NR_5R_5$, $-C(-CN)NO_2$, $-C(-CN)C(O)OR_{12}$ or $-C(-CN)C(O)NR_5R_5$;

or a pharmaceutically acceptable salt thereof; provided that m is 2 when R_{10} is OH in $(CR_{14}R_{14})n-C(O)O-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$, or $C(R_{14}R_{14})_sO(CR_{14}R_{14})_mR_{10}$ and further provided that at least one of the R_4 or R_{14} groups on (a) or (b) is not hydrogen when q is 0, R_3, $R_{3'}$, R_8 and X_3 are H; X is OR_2, X_2 is O and X_1 is O or S.

2. A compound of claim 1 wherein X_1 and X_2 are oxygen, A is (a), X is YR_2, Y is O and R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, tetrahydrofuran, cyclopentenyl, $-C_{1-7}$ alkyl, unsubstituted or substituted by one or more fluorines or chlorines; or $-(CH_2)_{2-4}OH$; R_2 is a C_{1-2} alkyl optionally substituted by one or more halogens, preferably fluorine or chlorine; one R_3 is hydrogen and the other R_3 is hydrogen, $C\equiv CR_9$, CN, $C(=Z)H$, CH_2OH, CH_2F, CF_2H, or CF_3; $R_{3'}$ is hydrogen, Z is O, NCN or NOR_5; X_3 is hydrogen; R_4 is H, Br, OR_{16}, CN, NR_5R_6, NO_2, $C(O)R_7$, $S(O)_mR_{12}$, 1- or 2-imidazolyl, $-OC(O)CH_3$ or $NHC(O)R_{15}$; R_8 is C(O)OH, H or C(O)OEt; and R_{14} is hydrogen, CH_3, NH_2 or $NHC(O)CH_3$.

3. A compound of claim 1 wherein R_1 is C_{1-4} alkyl substituted by 1 or more fluorines, CH_2-cyclopropyl, CH_2-cyclopentyl, cyclopentyl or cyclopentenyl, R_2 is methyl or fluoro substituted C_{1-2} alkyl; R_3 is hydrogen, $C\equiv CH$ or CN; and R_4 is hydrogen, Br, NH_2, $NHC(O)CH_3$, C(O)OH, $NHC(NCN)SCH_3$, $NHC(O)NH_2$, $N(CH_3)_2$, $NHC(O)C(O)OCH_3$, $NHC(O)C(O)OH$, $NHS(O)_2CH_3$, $C(O)OCH_3$, $S(O)_2CH_3$, SCH_3, $NHC(O)C(O)CH_3$, $S(O)CH_3$, $NHC(O)C(O)NH_2$, CN, $C(O)NH_2$, $NHS(O)_2CF_3$, $C(NH)NH_2$, $O-C(O)CH_3$, $-C(O)N(CH_3)_2$, 1- or 2-imidazolyl, $-NHC(O)CH_2Cl$, -NHC(O)-oxazolidinyl, -NHC(O)-4,4-dimethyl-oxazolidinyl or OH.

4. A compound of claim 1 wherein R_1 is cyclopentyl, CF_3, CH_2F, CHF_2, CF_2CHF_2, CH_2CF_3, CH_2CHF_2, CH_3, CH_2-cyclopentyl, CH_2-cyclopropyl or cyclopentenyl; R_2 is CF_3, CHF_2, or CH_2CHF_2; one R_3 is hydrogen and the other R_3 is hydrogen, C≡CH or CN and is in the 4-position; one R_4 is hydrogen and the other is $NHC(O)CH_3$, NH_2, $NH-C(=NCN)SCH_3$, $NHC(O)CO_2CH_3$, $C(O)OCH_3$, $NHC(O)NH_2$, or $NHC(O)C(O)CH_3$, $NHC(O)C(O)NH_2$; or wherein both R_4 groups are NH_2 or $NHC(O)CH_3$; R_8 is hydrogen and R_{14} is hydrogen.

5. A compound of claim 1 selected from the group consisting of:

(S)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(S)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

R-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

1-(4-Oxamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diacetamidobenzyl)-2-pyrrolidinone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diaminobenzyl)-2-pyrrolidinone;

1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone;

1-(4-N-Carbomethoxycarbamidobenzyl)-4-)3-cyclopentyloxy-4-ethoxyphenyl)-2-pyrrolidone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-N-[ureido]benzyl-2-pyrrolidone; and

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-pyruvamidobenzyl)-2-pyrrolidinone.

6. A pharmaceutical composition comprising a compound of claims 1-5 and a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1 to 5 for use in the inhibition of the production of tumor necrosis factor (TNF) or prevention of a TNF mediated disease state.

8. A compound according to any one of claims 1 to 5 for use in inhibiting phosphodiesterase IV.

9. A compound according to any one of claims 1 to5 for use in the treatment of allergic and inflammatory diseases.

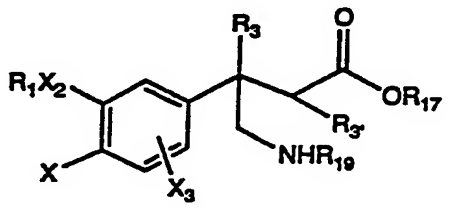
10. Use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for use in the inhibition of the production of tumor necrosis factor (TNF) or prevention of a TNF mediated disease state.

11. Use of a compound of Formula (I) as defined in claim 1 in the manufacture of a medicament for use in inhibiting phosphodiesterase IV.

12. Use of a compound of Formula (I), as defined in claim 1, in the manufacture of a medicament for use in the treatment of allergic and inflammatory diseases.

13. A process for producing a compound of Formula (I) according to claim 1 which process comprises:

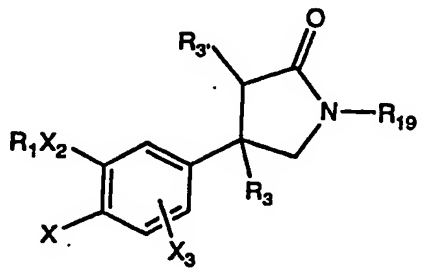
a) reacting a compound of Formula (7)



wherein R_{19} is H, R_{17} is an alkyl or aryl group, $R_{3'}$ is H or $C(O)OR_{17}$, R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9, R_1, X_2, X and X_3 are as defined in Formula (I) or are groups convertable to such, with an appropriate aldehyde followed by reduction of the imine to provide compounds of Formula (7) wherein R_{19} is $CH_2(CH_2)_mA$, which are further cyclized to provide compounds of formula I; or

(b) compounds of Formula (7) wherein R_{19} is H are treated with appropriate activated alkylating agents, with or without a catalyst, to provide compounds of Formula (7) wherein R_{19} is $CHR_8(O)_q(CH_2)_mA$ which are cyclized to provide compounds of Formula (I); or

(c) compounds of Formula (7) wherein R_{19} is H are cyclized to provide compounds of Formula 8



wherein R_{19} is H, which are further reacted with a strong base, followed by reaction with an appropriate activated alkylating agent to provide compounds of Formula (I), or

(d) for compounds of Formula (7) wherein R_{19} is H and R_3 is $CONH_2$, the compound is first protected at R_{19} with a suitable protecting group, followed by amide dehydration, followed by removal of the protecting group to provide compounds of the Formula (7) wherein R_{19} is H and R_3 is CN, which are then cyclized to provide compounds of Formula (I), wherein R_3 is CN, and X and X_3 are other than $S(O)_mR_2$, Br, I, NO_2 or foramide, or

(e) for compounds of Formula I wherein R_3 is OR_5, a compound of Formula (7) wherein R_{19} is H and R_3 is the protected or unprotected hydroxyl is alkylated on nitrogen and cyclized; or

(f) for compounds wherein R_3 is F the compounds of (e) are further treated with diethylamino sulfur trifluoride to provide the desired compound; or

(g) compounds of Formula (I) wherein R_3 represents the remaining R_3 groups of Formula (I), may be derived from the compounds of Formula (I) or (8) wherein R_3 is CN by protection of the amide and other sensitive functionalities, then reduction of the R_3 CN group to CHO followed by further transformation of the CHO group to the desired group to give a compound of Formula I.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03613

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) C07D 207/26 A61K 31/40

US CL :548/543,548/550 548/551; 514/424

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : N/A

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	GB,P, 1,350,582, Strubbe et al. (18 April 1974) See entire document in particular Formula (I) page 1, col. 1, 2nd species 18, lines 31 and 32 on page 11, col. 1, showing 4+ 10-Meophenyl-3 me pyrrolidone-2, and claim 56 showing pyrrdidone-2 ring formatin from 3 -cyano propornic acid esters.	1-9 13
Y	AU,P, 201,369 (Frick) (10 February 1955) See entire doucment essentially direct to formation of 4,4-disubstituted pyrrolid-2- ones by catalytic hydrogenation of beta-cyano propionates.	13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 10 JUNE 1992	Date of mailing of the international search report 16 OCT 1992
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